HYPERURICEMIA AS AN ADDED RISK FACTOR FOR MICROVASCULAR COMPLICATIONS IN DIABETIC PATIENTS

Dissertation Submitted to

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

In the fulfilment of the regulations for the award of the degree

by

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THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

APRIL 2017

CERTIFICATE

This is to certify that the thesis entitled **"HYPERURICEMIA AS AN ADDED RISK FACTOR FOR MICROVASCULAR COMPLICATIONS IN DIABETIC PATIENTS"** is a bonafide work of **Dr. PRASHANTH ARUN** done under the direct guidance and supervision of **Dr. SUJAYA MENON, M.D.,** in the department of General Medicine, PSG Institute of Medical Sciences and Research, Coimbatore in fulfilment of the regulations of Dr.MGR Medical University for the award of MD degree in General Medicine.

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DECLARATION

I hereby declare that this dissertation entitled **"HYPERURICEMIA AS AN ADDED RISK FACTOR FOR MICROVASCULAR COMPLICATIONS IN DIABETIC PATIENTS" was** prepared by me under the direct guidance and supervision of **Dr. SUJAYA MENON, MD.,**PSG Institute of Medical Sciences and Research, Coimbatore.

The dissertation is submitted to the Tamil Nadu Dr. MGR Medical University in fulfilment of the University regulation for the award of MD degree in General Medicine. This dissertation has not been submitted for the award of any other Degree or Diploma.

Dr. PRASHANTH ARUN

CERTIFICATE BY THE GUIDE

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PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

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To
Dr Prashanth Arun
Postgraduate
Department of General Medicine
PSG IMS & R
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Ref: Project No. 14/429

Date: March 4, 2015

Dear Dr Prashanth Arun,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 10.12.2014 to conduct the research study entitled *"Is hyperuricemia an added risk factor for microvascular complications in a diabetic patient?"* during the IHEC meeting held on 12.12.2014.

The following documents were reviewed and approved:

1. Project Submission form
2. Study protocol
3. Informed consent forms [ver 1.1]
4. Proforma
5. Current CVs of Principal investigator, Co-investigator
6. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 12.12.2014 at IHEC Secretariat, PSG IMS & R between 10.00 am and 11.00 am:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the institution Yes/No	Present at the meeting Yes/No
1	Dr. P. Sampath (Chairperson, IHEC)	DO, DNB	Clinician (Ophthalmology)	Male	No	Yes
2	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
3	Dr. S Shanthakumari	MD	Pathology, Ethics	Female	Yes	Yes
4	Dr. D. Vijaya	M.Sc, Ph.D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

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Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval
   d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented
   e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented
   f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review
7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Thanking You,

Yours Sincerely,

Dr S Bhuvaneshwari
Member-Secretary
Institutional Human Ethics Committee

ACKNOWLEDGEMENT

The successful completion of my dissertation would not have been possible without the contribution of many people to whom, I would like to express my deep sense of gratitude.

First and foremost, I am very much thankful to my guide **Prof. Dr. SUJAYA MENON,** for her scholarly advice, valuable guidance and meticulous scrutiny at various stages of my dissertation.

I am highly indebted and thoroughly grateful to **Prof. Dr.K. JAYACHANDRAN,** for being a constant source of motivation. His fine teaching skills helped me build a strong foundation in the subject.

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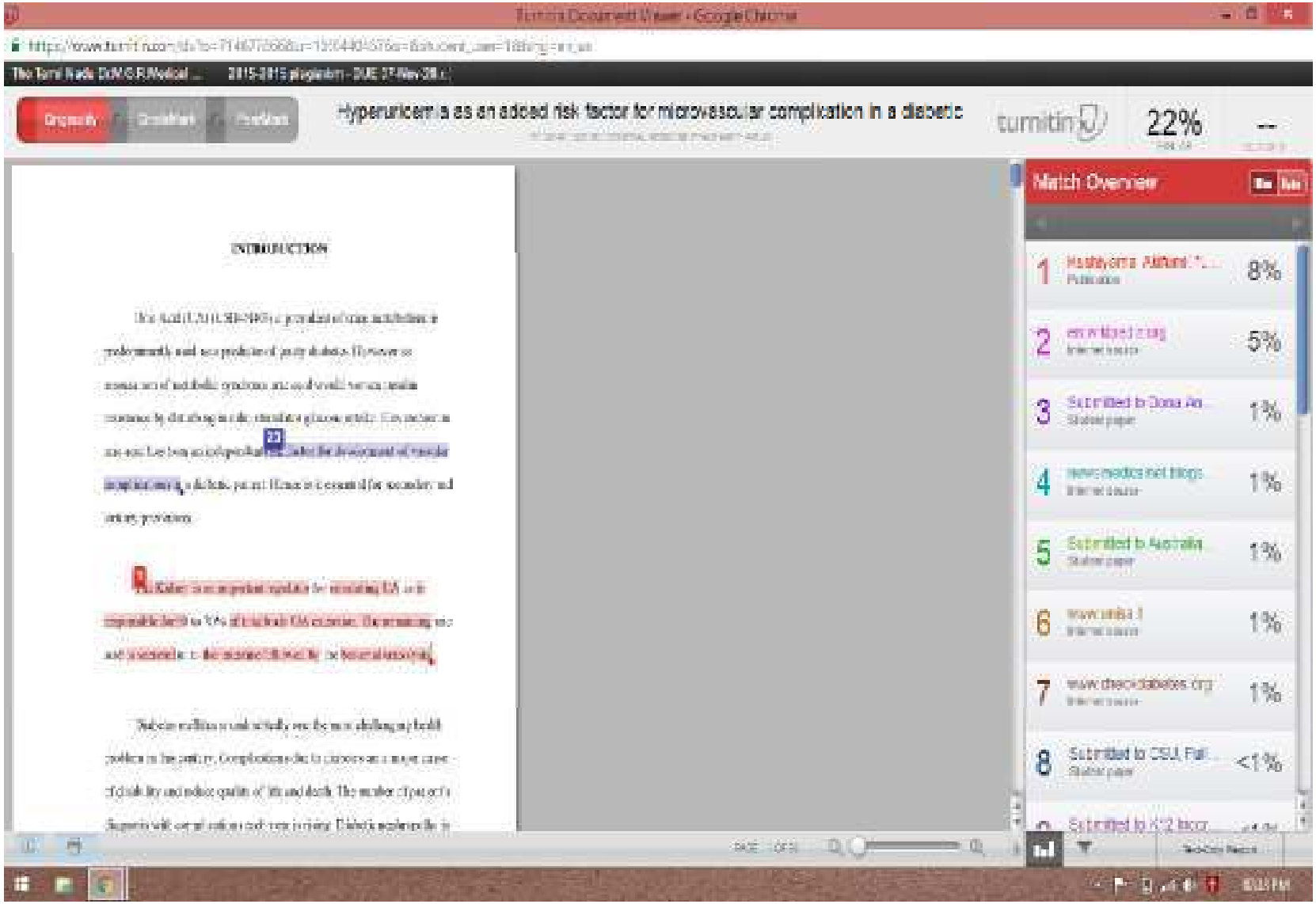
I would take this as a great opportunity to thank all my patients without whose consent, I would not have been able to complete this study.

Above all, I would like to exceptionally thank **Dr.Anirudh Somani** and **Dr. Ashwini Annabathula** for the great moral support and motivation throughout the period of my post-graduation and for being true friends and for always lending a helping hand.

I would be failing in my duty if I do not immensely thank my beloved parents for making me what I am.


Hyperuricemia as an added risk factor for microvascular complication in a diabetic
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INTRODUCTION

CONTENTS

TITLE

Hyperuricemia as an added Risk Factor for Microvascular Complications in Diabetic Patients

INTRODUCTION

Uric Acid (UA) (C5H4N403) a prevalent of urine metabolism is predominantly used as a predictor of gouty diabetes. However as association of metabolic syndrome uric acid would worsen insulin resistance by disturbing insulin stimulator glucose uptake. Elevatedserum uric acid has been an independent risk factor for development of vascular complications in a diabetic patient. Hence is it essential for secondary and tertiary prevention.

The kidney is an important regulator for circulating UA as is responsible for 60 to 70% of total body UA excretion. The remaining uric acid is secreted in to the intestine followed by the bacterial uricolysis.

Diabetes mellitus is undoubtedly one the most challenging health problem in this century. Complications due to diabetes are a major cause of disability andreduce quality of life. The number of patientdiagnosed with complications each year is rising. Diabetic nephropathy is the leading cause of death for people with Type 2DM.

Vascular complications of diabetes mellitus or classified in to microvascular and macro vascular complications.

Microvascular Complications:

- Diabetic Nephropathy
- Diabetic Neuropathy
- Diabetic Retinopathy

Macrovascular Complications:

- Coronary Diseases
- Cerebrovascular Diseases
- Peripheral Vascular Diseases

Diabetes Mellitus

- FBS greater or equal 126mg/dl
- PPBS greater or equal 200mg/dl
- HbA1c greater or equal 6.4
- Diabetic Retinopathy - Fundus Examination
- Diabetic Neuropathy - General Physical Examination, Neurological Examination
- Diabetic Nephropathy - Microalbuminuria, Creatinine levels.

AIM

To assess the effect of Hyperuricemia as an added risk factor for microvascular complications in diabetic patients.

MATERIALS AND METHODS

Types of Study: Hospital based observational study

Place of Study: PSG Hospital, PSG IMS&R, Coimbatore

Duration of Study: One year (April 2015- April2016)

INCLUSION CRITERIA:

- Diabetic patients diagnosed by ADA criteria
- Age 20 to 80 years
- Male and female

EXCLUSION CRITERIA:DKA/HONK

- GDM
- Acute onset of disease
- CKD

Methodology:

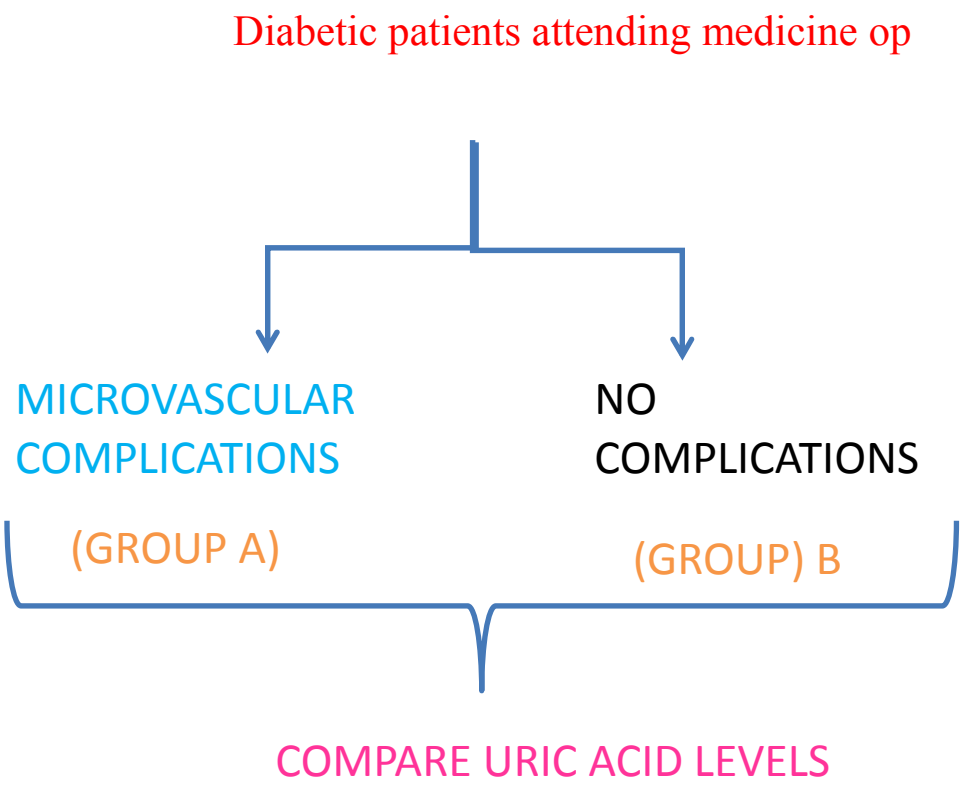
- Obtained consent from all those who participated in this study.
- This study was based on observational collection of data of diabetic patients with and without microvascular complications.
- Patients underwent a history taking with general physical examination. (Age, sex, duration of disease)
- Patients were scanned for diabetes by ADA criteria.
- Patients were examined for vascular complications.
- We divided them into 2 groups.

I. **Group I:**Patients with diabetes without vascular complication

II. **Group II:** Patients with diabetes and vascular complications.

- Uric acid levels were observed for both the groups
- Age, sex, duration of the disease was all most equal in both the groups.

Result were computed to see if Hyperuricemia was an added risk factor for vascular complications in diabetic patients.


Diabetic patients attending medicine op
MICROVASCULAR COMPLICATIONS
NO COMPLICATIONS
(GROUP A)
(GROUP) B
COMPARE URIC ACID LEVELS

Patients are examined in detail and they are diagnosed diabetic based on ADA criteria.

	Pre-Diabetes	Diabetes
FPG*	100-125 mg/dL 5.6 mmol/L – 6.9 mmol/L	126 mg/dL and over 7.0 mmol/L and over
OGTT* after 75 g glucose load	140 mg/dL - 199 mg/dL 7.8 mmol/L – 11.0 mmol/L	200 mg/dL and over 11.1 mmol/L and over
A1c†	5.7 % - 6.4%	6.5% and over

*FPG and OGTT guidelines for GDM are different;†A1c does not apply to diagnosis of type 1 diabetes or to GDM.

Diabetic complications were diagnosed by:

Diabetic retinopathy: Fundus examination (ophthalmologist) , medical records, diagnosed by a medical practitioner.

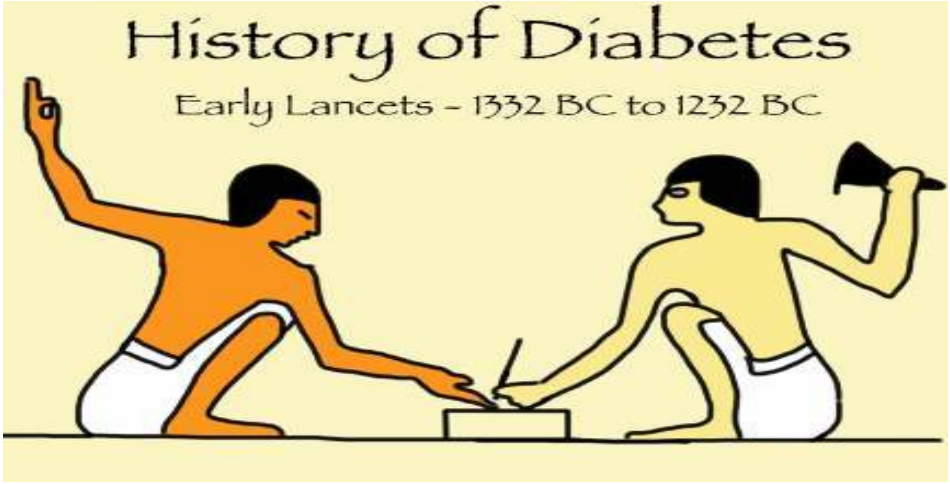
Diabetic neuropathy: nylon monofilament,general physical examination, medical record, diagnosed by a medical practitioner.

Diabetic nephropathy: albuminuria, creatinine, medical records, diagnosed by a medical practitioner.

REVIEW OF LITERATURE

History:

Diabetes Mellitus was one of the earliest diseases portrayed (1) in an Egyptian Manuscript from around 1500 BC, the first described case being type 1 DM. (2)



Around the same time, Indian physicians termed it “Honey urine”. The term diabetes was first used by the Greek God Apollonius of Memphis. The disease prevalence at that time was low probably due to the diet and life style followed by the people of that time.

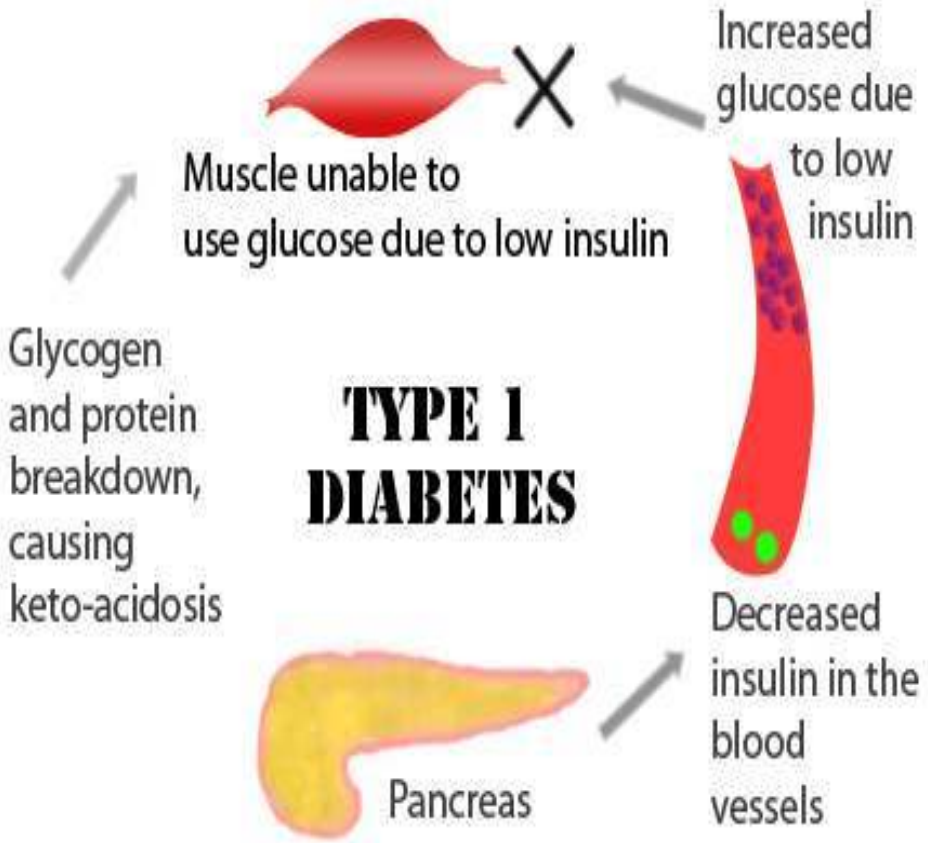
Effective treatment for diabetes was not developed until the early part of the 20thCentury. Diabetesmellitus ,colloquially referred to asdiabetes is a multi-system metabolic disease in which there is high plasma sugar level(3).

Diabetes is caused by reduced amount of production of insulin by the pancreatic islets or due to peripheral receptor level resistance to insulindespite adequate circulating insulin levels (4).

Traditionally, Diabetes Mellitus has been classified as follows:

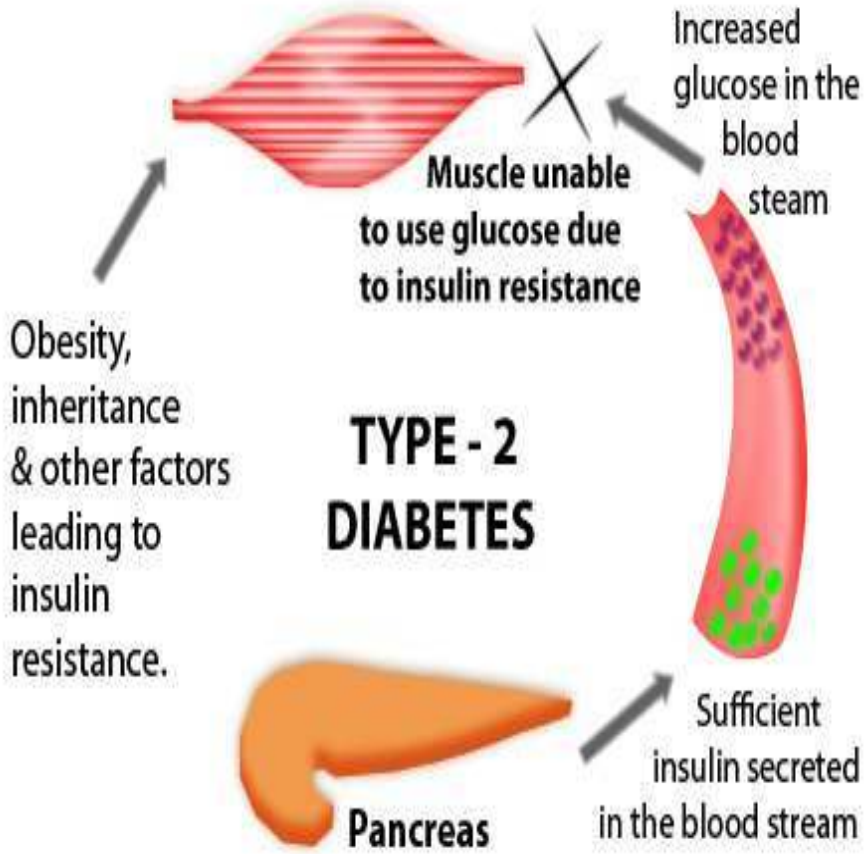
Type1DM:

Type 1 DM results from an inadequate production of insulin from the beta cells of Islets of Langerhans. It was previously referred to as insulin dependent or juvenile diabetes but this term is redundant nowadays. The cause of this type is thought to be of auto-immune in etiology.



Type II DM:

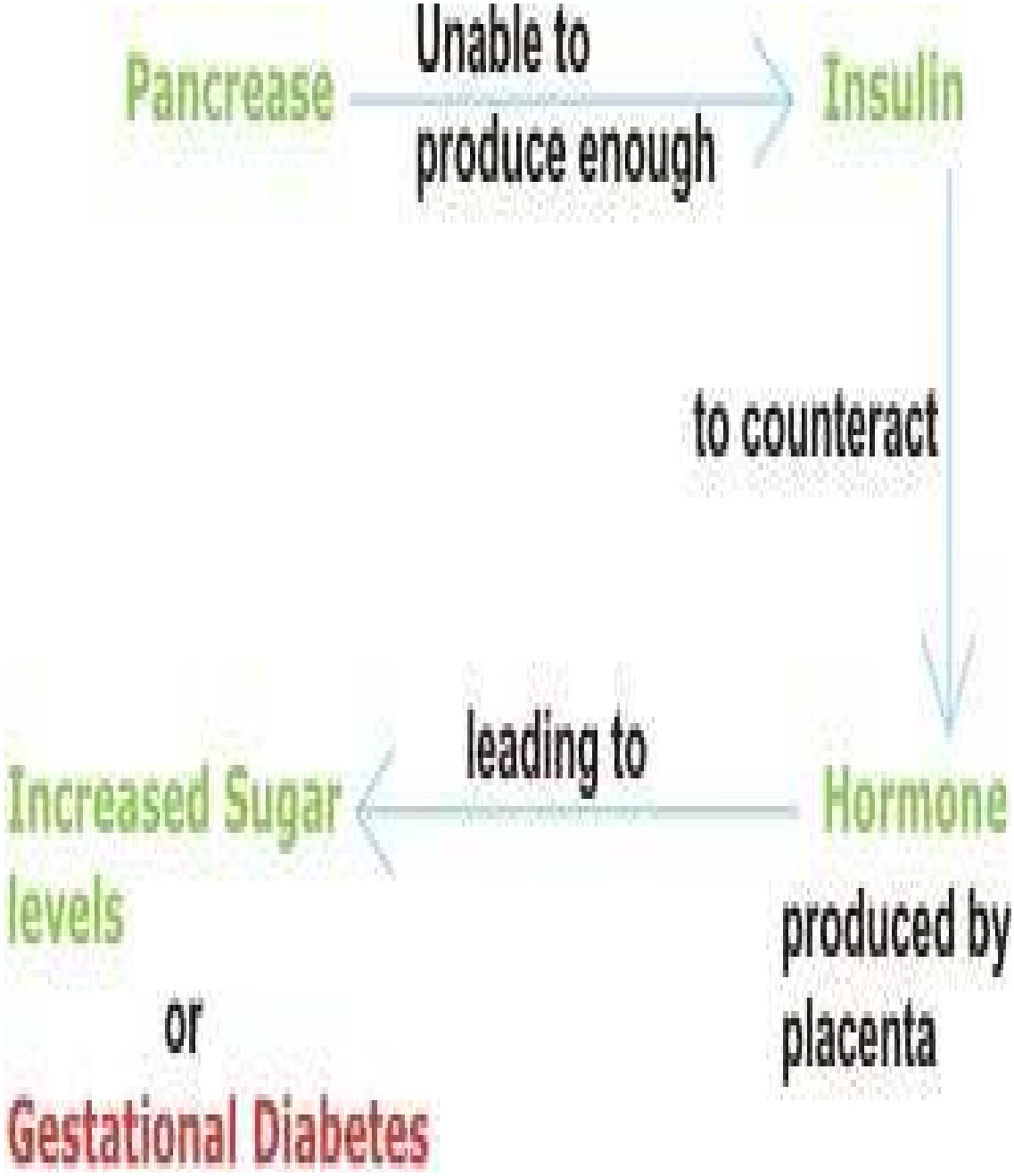
Primarily caused due to the receptor level resistance to insulin which arises due to a multitude of reasons, predominantly life-style related. As the disease progresses, this state of relative insulin deficiency becomes an absolute insulin deficient state.

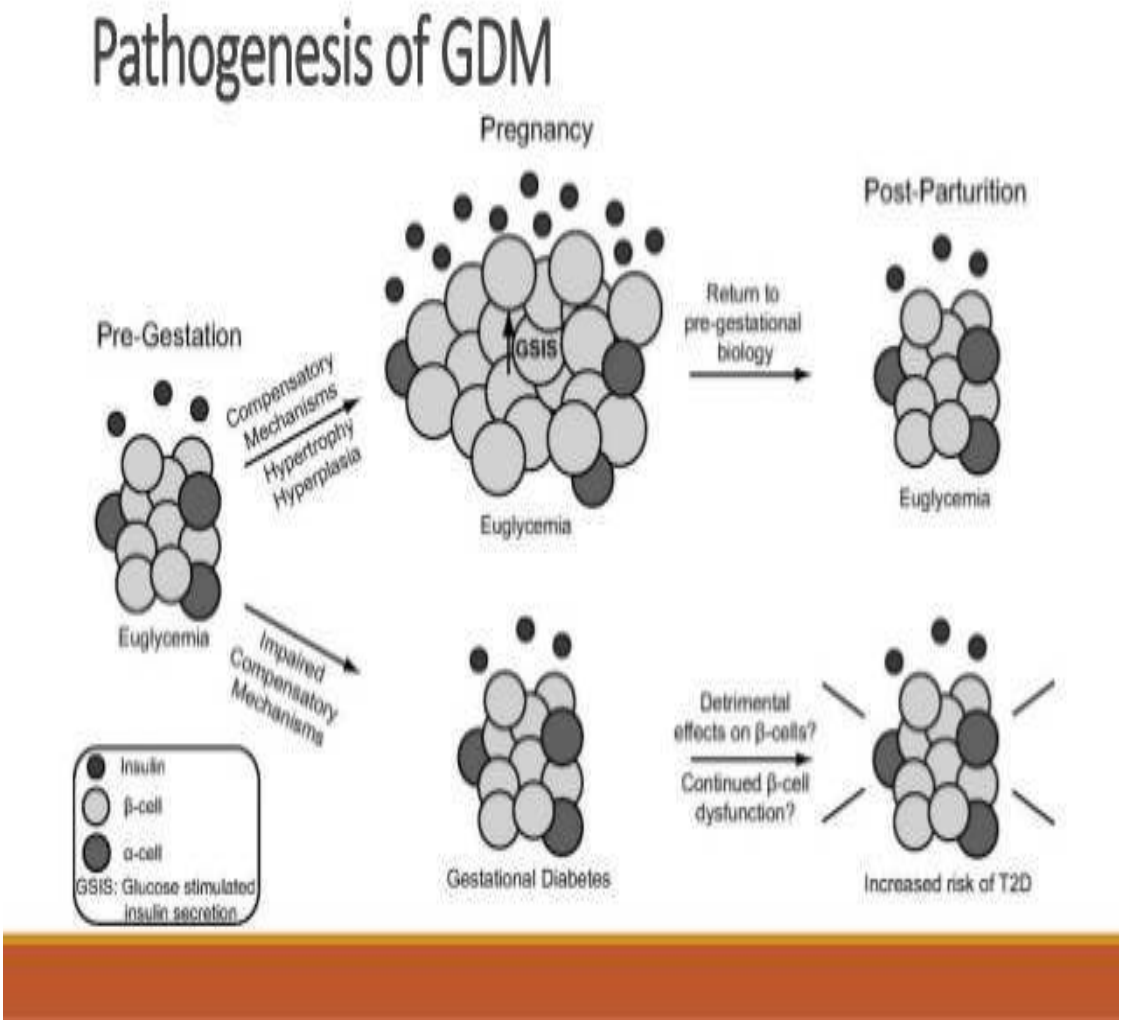


Gestational Diabetes:

The third main form occurs when pregnant women who previously did not have diabetes develop high blood sugar levels.

As of 2015, an estimated 415 million people had diabetes ([6]). T2DM constitutes 90% of the cases (7, 8) and the prevalence among men and women were found to be comparable (9). The global economic cost of diabetes in 2014 was estimated to be USD 612 million[10].


Pancrease
Unable to produce enough
Insulin
to counteract
Hormone produced by placenta
leading to
Increased Sugar levels
or
Gestational Diabetes


Pathogenesis of GDM
Pregnancy
Post-Parturition
Pre-Gestation
GSIS
Return to pre-gestational biology
Compensatory Mechanisms
Hypertrophy
Hyperplasia
Euglycemia
Euglycemia
Euglycemia
Impaired Compensatory Mechanisms
Detrimental effects on β-cells?
Continued β-cell dysfunction?
Insulin
β-cell
α-cell
GSIS: Glucose stimulated insulin secretion
Gestational Diabetes
Increased risk of T2D

Other types of Diabetes Mellitus:

Pre diabetes indicates a state in which a person's blood glucose levels are higher than normal values but not high enough to qualify for a diagnosis of diabetes mellitus.

LADA (Latent autoimmune diabetes of adults): Is a condition in which Type 1 DM – like picture develops in an adult. Adults with LADA are frequently misdiagnosed as having Type2 DM.

Type III Diabetes:

Is a term that is suggested for Alzheimer's disease as the pathogenesis may involve insulin resistance in the brain[15].

The following is a comprehensive list of other causes of diabetes [16]

- Genetic defects
- Genetic defects in insulin processing and action
- Exocrine pancreatic defects
- Environmental factors
- Infections
- Drugs

Signs and Symptoms:

The classicalcluster of symptoms of untreated diabetes are

- Weight loss
- Polyuria
- Polyphagia
- Polydipsia [11].

Symptoms may develop rapidly in type I DM, while they are slow to evolve in Type II DM.

Several signs and symptoms can signal the onset of diabetes although they are not specific to the disease.They include

- Blurred vision
- Head ache
- Fatigue
- thirst
- Slow healing of wounds
- Itchy skin.
- Hunger
- Vaginal Infections

- Sudden weight loss
- Tingling sensation of hands and legs
- Frequent urination

DIABETIC EMERGENCIES:

Hypoglycemia:

Low blood sugar (<60mg/dl) is considered to be hypoglycaemia. It is common in people with type I DM& type II DM on treatment. Effects can range from an uneasy feeling,sweating, trembling, increased appetite, change in behaviour to unconsciousness, coma and death. "Hypoglycemic unawareness" is a term that is applied to patients who do not experience any of the above-mentioned symptomsdespite profound hypoglycaemia, resulting from blunted autoimmune response in long-term diabetics.

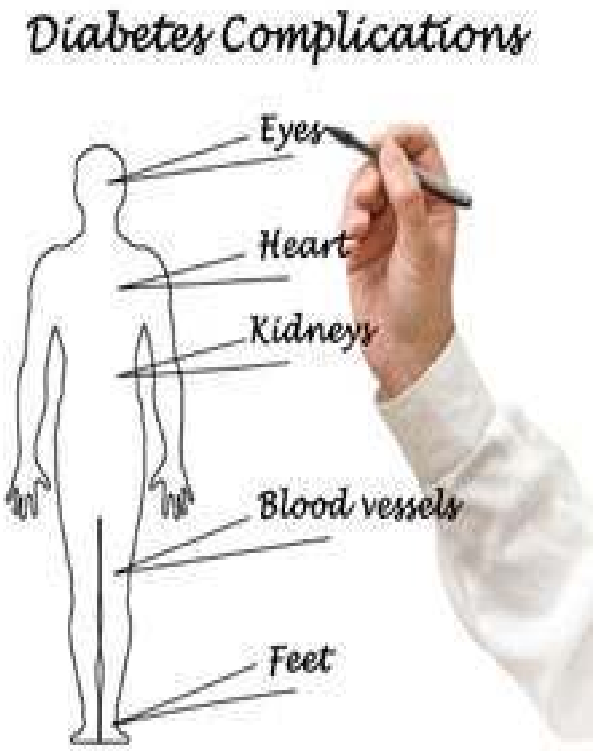
Diabetic Ketoacidosis:

Patients with Type 1 DM might develop diabetic Ketoacidosis which is a metabolic disturbance characterised by nausea and vomiting,acidotic breathing, Kussmaul's breathing, dehydration and decreased consciousness (12). It is characterised by blood sugar levels of more than 400mg/dl. A condition called Hyper-osmolar non-ketotic coma (HONK) is more common in Type 2 DM patients.

CHRONIC COMPLICATIONS OF DIABETES MELLITUS:

The main chronic complications of Diabetes Mellitus include damage to the microvasculature.

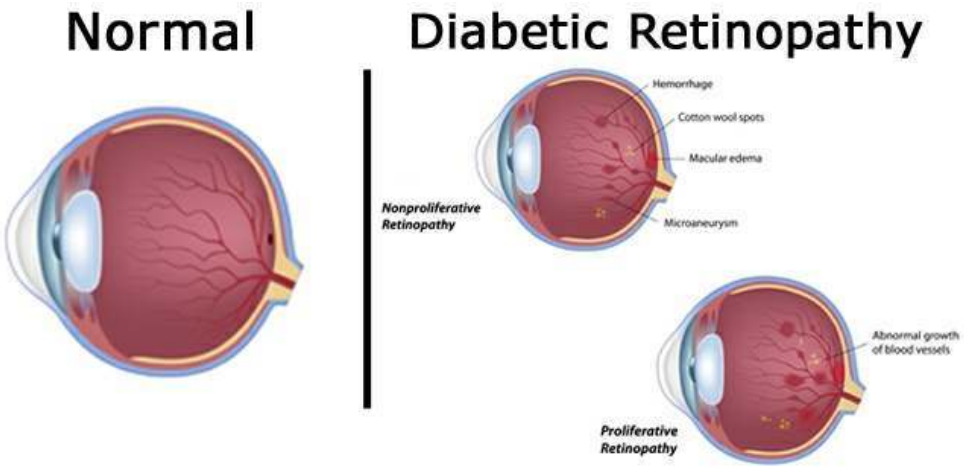
The next major set of complications of Diabetes Mellitus include damage to the larger vessels of the cardiovascular, cerebrovascular & peripheral vascular systems (13).



MICROVASCULAR COMPLICATIONS:

Eye- Diabetic Retinopathy

Diabetic Retinopathy is growth of friable neo-vasculature in the retina as well as macular oedema which can lead to severe vision loss. The presence of Diabetic Retinopathy is associated with visceral fat accumulation and insulin resistance in T2DM patients. An earlier study showed no significance difference in uric acid levels between patients with and without retinopathy (14).Retinal damage makes it the most common cause of blindness among non-elderly subjects.



Blindness can be caused due to

- Non resolving vitreous hemorrhage
- Tractional retinal detachment
- Diabetic macular edema

Patients may be asymptomatic in the early stages

Risk factors:

- Duration of diabetes
- Bad glycemic control
- SHT
- Nephropathy
- Obesity
- Smoking

Classification:

- Non proliferative diabetic retinopathy
- Proliferative diabetic nephropathy
- Clinical significant macular edema

Non proliferative Retinopathy is further classified to:

- Mild
- Moderate
- Severe
- Very Severe

Non Proliferative diabetic retinopathy:

Mild:

- One micro aneurysm – earliest detectable lesion
- Retinal hemorrhage

Moderate:

- Micro aneurysm + Hemorrhage in atleast one quadrant
- Soft exudates
- Venous bleeding or intra retinal microvascular abnormalities

Severe:

- Micro aneurysm + Hemorrhage in atleast four quadrant
- Venous bleeding in two or more quadrant
- Moderate IRMA in at least one quadrant

Very Severe:

Any two features of 4-2-1 rule

Proliferative retinopathy:

Proliferation of new vessels, usually veins

- New vessels on optic disk
- New vessels elsewhere on retina

Clinical significant macular edema:

- Edema at the macula
- Dimness of vision
- Retinal edema close to fovea

Causes:

- Damage of blood vessels of retina
- Microvascular leakage and occlusion
- Micro aneurysm – out pouching of weakened capillary wall
- Mild to moderate damage of blood vessels leaks fluid into retina (causes edema and exudates)

Microvascular occlusion

↓

Hypoxia of retina

↓

Re- establish circulation

↓

Vascular endothelial growth factor

↓

Neovascularization

↓

Bleeding

Complications:

- Vitreous hemorrhage
- Retinal detachment
- Glaucoma
- Rubeosisiridis

Management:

Basic:

- Control of disease
- Associated factors Lipids, renal failure, Systemic hypertension
- Risk factors to be avoided (slows the progression of disease)

Mild and moderate:

- No specific treatment
- Control of diabetes
- Fundus examination

Severe and very severe:

- Close follow up with ophthalmologist
- Laser photo coagulation
- Cataract surgery

Clinically significant macular edema:

1. Focal or grid laser photo coagulation

   Laser (OP procedure)

   ↓

   Seals the leaking vessels from macula

   ↓

   Away from fovea

2. Optical coherence tomography – non invasive
3. Anti VEGF or intra vitreal injection of steroids

Proliferative diabetic retinopathy:

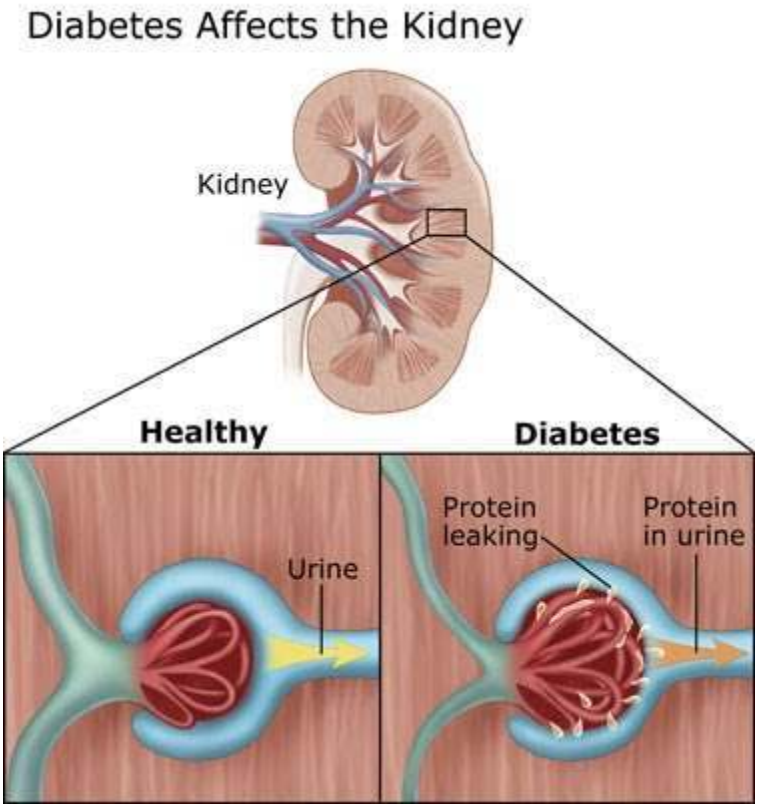
- ✓ Laser photo coagulation
- ✓ Pan retinal photo coagulation

Surgical intervention:

- Victrectomy (Remove exudates and clear hemorrhage)

DIABETIC NEPHROPATHY:

Damage to the kidney can lead to chronic renal failure eventually requiring dialysis. Diabetic mellitus is one of the most common causes of CKD. The typical pathological feature is Nodular Glomerulosclerosis, also called as Kimmelstein-Wilson disease. It also results in mesangial sclerosis.



Clinical syndrome:

- Persistent albuminuria > 300mg / 24 hrs urine or > 200 mcg / min
- Also called as macroalbuminuria
- Microalbuminuria: 30 to 300 mg/dl/ 24 hrs

Risk factors:

- Familial
- Polymorphism in angiotensin converting enzyme gene.
- Male
- Type II DM after the age of 50
- Systemic hypertension
- Obesity
- Smoking

Classification:

Classified into 5 stages:

- Stage of renal hypertrophy and glomerular hyperfiltration
- Stage of apparent normalcy
- Stage of microalbuminuria
- Stage of overt nephropathy
- End stage renal disease

Stage I:

Uncontrolled blood sugar

↓

Increased GFR, renal hypertrophy

↓

Insulin therapy

↓

Return to normal

Stage II:

Silent + glomerular hyperfiltration

↓

Blood sugar >250mg/dl

↓

Decreased GFR

Stage III:

- Important as it is reversible
- 6 to 15 years after diabetes
- Albumin 3 to 300 mg/dL /24 hrs
- Increased blood pressure
- Loss of dipping of nocturnal blood pressure

Stage IV:

- Irreversible
- 15 to 18 years of DM
- GFR starts to decline at this rate (10ml/ min/year)
- Microscopic hematuria
- Nephrotic syndrome is seen

Stage V:

- 25 years of DM
- GFR declines further more (20ml/ min/year)

Pathogenesis:

Hyperglycemia:Sorbitol pathway causes injury to the kidney

Hypertension: Stress on the kidney that causes accumulation of protein in tubular cells that causes proteinuria.

Screening:

- Yearly screening of diabetics
- Three times a year to check microalbuminuria (Preferably over night sample)

- Random urine albumin to Creatinine ratio -collection in dipstick method

When to look for differential diagnosis:

- Absence of retinopathy
- Sudden proteinuria without albuminuria
- Macroscopic hematuria
- Decline of GFR without proteinuria

Management:

Prevention is better

- HbA1c<7% is best for reducing microalbuminuria

Primary prevention:

- From happening at all

Secondary prevention:

- Removing factors that progress kidney disease

Tertiary prevention:

- Proper management of CKD

Control of Hypertension:

- Maintain BP at 130/85 – 125 / 75 in proteinuria patients
- In the Absence of proteinuria maintain BP at (130/80)
- Antihypertensives reduced mortality
- ACE and ARB should be the drug of choice.

Dietary Restriction:

- Calories restriction
- Proteins 0.8gms/ kg/ day
- Potassium restriction 0.9gm/ kg/ day
- Salt restriction
- Avoid NSAIDS and aminoglycosides

Monitor

- GFR assessment monthly

Supportive treatment:

- Life style modification
- Control of dyslipidimia
- GFR <60ml

Treatment for Anemia:

Hemoglobin to be inbetween 11 to 12 gm/dl

Erythropoietin in the dose of 50 to 150 units/kg/week is needed in CKD stage 4 and 5

Renal replacement therapy:

i. GFR <20ml/ min

ii. Arterio-venous fistula

iii. Hepatitis B Vaccination

iv. Hemodialysis

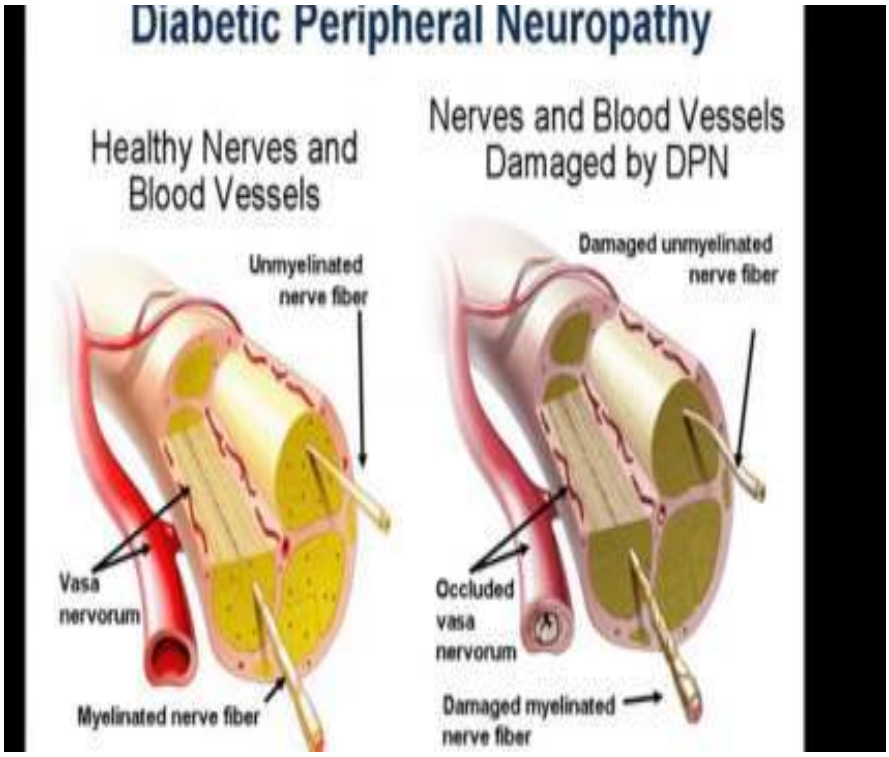
v. Peritoneal dialysis

vi. Transplantation

DIABETIC NEUROPATHY:

Abnormal and decrease sensational: usually in a glove and stocking distribution starting with the feet but can also involve other nerves, later the fingers and hands.

When combined with ischemic blood vessels can cause diabetic foot. Otherforms of neuropathy may present as mono neuritis.



Decline and damage of nerve function leading to loss of sensation

Ulceration

Amputation

Neuropathy can be due to axon damage or demyelination.

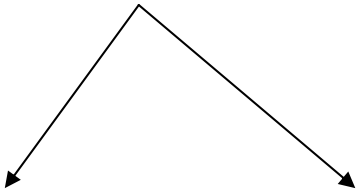
Axon damage may be due to subsequent regeneration of nerve fibers and may cause par aesthesis.

Risk factors:

- Poor glycemic control
- Duration of disease
- Damage of blood vessels
- Mechanical injury to nerves
- Genetic susceptibility
- Alcohol
- Smoking
- Cardio vascular disease

Classification:

- Sub clinical neuropathy
- Diffuse clinical neuropathy
- Focal neuropathy



Mono neuropathy Entrapment syndromes

Descriptive clinical classification:

Poly Neuropathy

- Sensory
- Motor
- Acute sensory
- Autonomic
- Proximal motor
- Truncal

Mono Neuropathy:

- Cranial

PATHOGENESIS

Metabolic hypothesis:

Persistent hyperglycemia + insulin deficiency

Alters sorbitol pathway

Increases advanced glycosylated end products

Increase oxidative stress

Nerve dysfunction

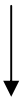
Immune hypothesis:

Auto antigens that induce immune response are anti phospholipids antibodies

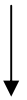
(Auto antibodies to gangliosides are seen to cause nerve dysfunction).

Microvascular hypothesis:

Impaired vasoconstriction and vasodilatation



Ischemia in nerves



Diabetic neuropathy

Neurotrophic hypothesis:

Neurotrophic factors like neurotrophin 3, neurotrophin 4/5,

IGF I which are all necessary for survival of neurons are deficient in hyperglycemia hence causes nerve damage.

Oxidative stress hypothesis:

Free radical formation due to hyperglycemia causes endothelial cell dysfunction which leads to nerve damage.

Small fiber neuropathy:

Involves alpha and c fibers

Sensory loss:

- Pin prick hypoesthesia
- Light touch sensation decrease
- Monofilament increased

Symptoms:

- Hyperalgisia (superficial pain +++)
- Decreased sweating
- Dryness of skin
- Severe hyperesthesia
- Hypoalgesia
- Shock
- Affected Areas: Glove and stocking
- No deformities
- Motor deficit absent
- Tendon refluxes or normal or decreased
- Foot ulceration and gangrene

Large fiber neuropathy:

- Delta type A
- Sensory loss is 0/ +++
- Decreased position sense
- Decrease muscle strength
- Reduced 2 point discrimination

Symptoms:

- Deep seated pain
- Dull aching pain
- Ataxia
- Fall
- Trauma
- Affected areas : lower limbs
- Small muscle wasting on feet
- Motor deficit +++
- Tendon reflex reduced
- Foot ulcer high risk
- Painful sensory neuropathy.

ASSESSMENT

Nylon monofilament:

- 2gms & 10gms (ADA)
- 2g-purple
- 10gms – red

Quantitative sensory testing:

- Vibration – tuning fork (128 HZ)

Proximal motor Neuropathy:

- Seen in Elderly
- Gradual in onset
- Pain followed by weakness
- Begins as unilateral then becomes bilateral
- Differential diagnosis: Chronic inflammatory demyelination.

MANAGEMENT

Small fiber Neuropathy:

- Foot inspection
- Sole mirror inspection
- MCR foot wear
- Well fit shoes
- No heat exposure
- Avoid fissures
- Nail should be cut transversely

Large fiber Neuropathy:

- Gait and strength training
- MCR

Medical management of DSPN:

Control of:

- Hyperglycemia
- BP
- Lipids
- Life style

Management of symptoms:

Paresthesia and dysaesthesia

- Tricyclic antidepressants (Amitriptyline)Contra indicated in CVDprostatic hyper trophy, glaucoma
- Anti-convulsants
- Carbamazepine 200-800mg / day
- Gabapentin 300-1800mg / day
- Pregabalin 150-600mg / day

Deep seated pain:

- Opioid derivatives (Tramadol)

Focal Neuropathy:

Mono neuropathy

- Seen in older patients
- Acute pain involves 3 and 6 cranial nerves
- Self limiting in 6-8 weeks

Treatment:

- Symptomatic and physiotherapy

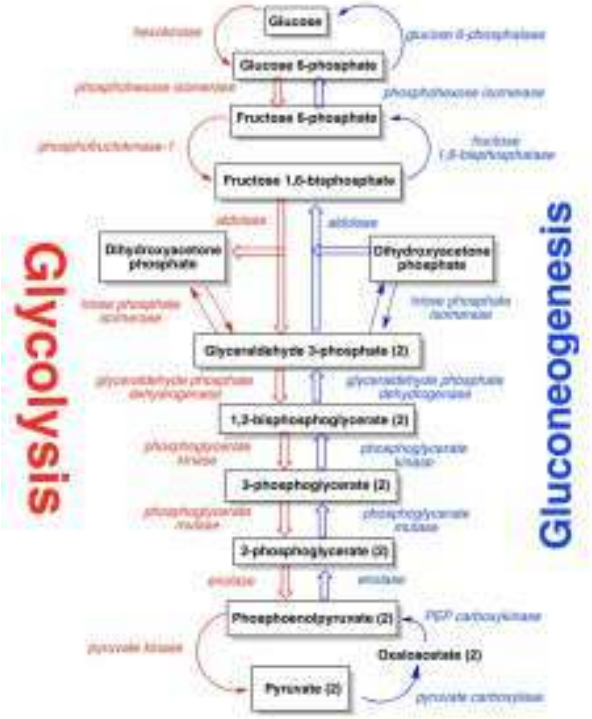
INSULIN

Is a principal hormone that helps in uptake of glucose from the blood into most cells of the body especially liver, muscle and adipose tissue. Hence insulin deficiency place a critical role in all forms of DM [17].

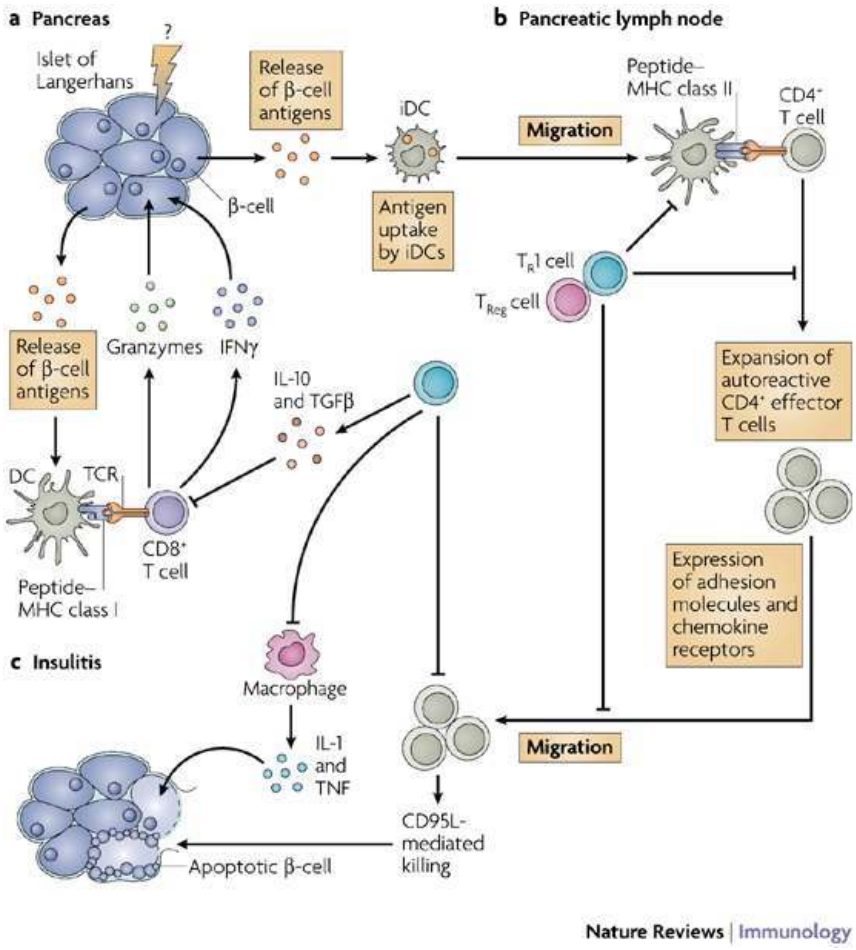
The body obtains glucose from four main places:

- The intestinal absorption of food
- The breakdown of glycogen,
- The storage form of glucose found in tissue
- Gluconeogenisis [18].

Insulin inhibits the process of the gluconeogenesis.



Insulin is released in to blood by β cells found in the islets of Langerhans in pancreas in response to raising levels of blood glucose. If the amount of insulin available is insufficient, cells respond poorly to effect of insulin or if the insulin itself is defective then glucose will not be absorbed properly by the body cells.[19]



When the glucose concentration in the blood remains high overtime the renal thresholdof reabsorption will be reached and glucose will be excreted [20].

This increasesosmotic pressure of urine and inhibits reabsorption of water by the kidney resulting in increased urine production and increasedfluids loss.

DIAGNOSIS

DM is characterised by the recurrent or persistent high blood sugar and is diagnosed by any of the following [21]

- Fasting Plasma glucose level ≥ 126mg /dl
- Plasma glucose ≥ 200 mg / dl 2hrs after a 75 g oral glucose load.
- Symptoms of High Blood sugar and RBS of ≥ 200mg /dl
- HBA1C ≥ 6.5% [22]

WHO recommendations for the diagnostic criteria for diabetes and intermediate hyperglycemia

	Impaired Fasting Glucose	Impaired Glucose Tolerance	Diabetes
Fasting plasma glucose	110-125 mg/dl	< 126 mg/dl	≥ 126 mg/dl
2 hour plasma glucose	< 140 mg/dl	140-199 mg/dl	≥ 200 mg/dl

Positive result should be confirmed by repeat of any of the above methods on a different day. It is preferable to measure a fasting glucose level because ofthe ease ofmeasurement.[23]According to current guidelines two fasting glucose measurements above 126mg/dl is considered for diagnosis for DM.

According to WHO criteria people with FBS [110-125mg/dl] are considered to have impaired fasting glucose [24].People with plasma glucose at or above 140mg/dl but not over 200mg/dl: two hours after a 75g diagnosed oral glucose load are diagnosed to have impaired glucose tolerance.

ADA since 2003 uses a slightly different range forimpaired fasting glucose of [100 to 125mg/dl][25].

	Year of Reports		
Criteria	**1979 and 1980**	**1997 and 1999**	**2003**
Fasting plasma glucose			
Diabetes	≥ 140 mg/dl	≥ 126 mg/dl	≥ 126 mg/dl
IFG	**	110–125 mg/dl	100–125 mg/dl
2-hour plasma glucose *			
Diabetes	≥ 200 mg/dl	≥ 200 mg/dl	≥ 200 mg/dl
IFG	140–199 mg/dl	140–199 mg/dl	140–199 mg/dl

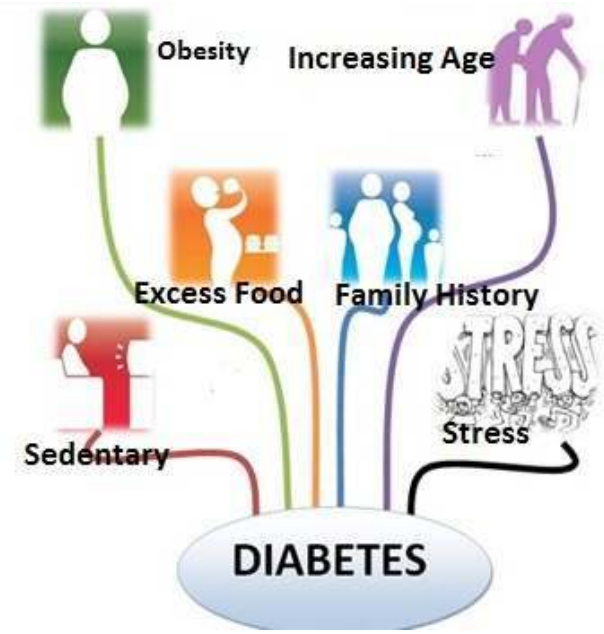
*2-hour 75-g OGTT
**Not considered

HbA1c is better than fasting glucose for determining risk of CVD and other death causes [26]

PREVENTION:

There is noknown preventive measure for type1 diabetes [27]

Type II diabetes which accounts for 85-90% of all cases can often be prevented or delayed byengaging in physical exercise and consuming a healthy diet. Higher level of physical activities reduces risk of diabetes by 28% [28].Tobacco smoking is also associated with the increased risk of diabetes cessation can be taken as a preventive measure [29]



MANAGEMENT:

Diabetes is a chronic illness for which there is no cure [30]

Management mainly concentrates on maintaining close to normal blood sugar levels without causinghypoglycemia.Knowing about the diseases is very important in the treatment. Complications are less common in patient with good control [31 and 32]

The goal in diabetes is aHbA1C ≥6.5.Other complications of diabetes should be monitored. Habits like smoking, increased cholesterol, fat, high BP should be controlled. Special foot wear available for patient with diabetes to reduce ulceration[33].

Life style modification playsa major role in diabetes patients. Central Obesity plays a major role in complications. Life style modification helps in reducing blood pressure[34].

Diabetic medications are available in different forms oral, injectable. Oral is Metformin, sulphonyl urea, GLP-1 agonist, thiazoledinediones SGLT2 inhibitors. Type2 DM is usually treated with Metformin and other drugs. There are studies that show it reduces mortality[35] Metformin works by reducing glucose production in the liver [36]

Oral drugs usually increase insulin release, reduce absorption of sugar from intestine and make the body more sensitive to insulin. While using injectable long acting is used first and then changed over to oral forms [37]Blood pressure monitoring is the most important in diabetic patient as cardio vascular disease is a serious complication. [38]

It is harmful treating BP less than 140 mmHG [39]. Among drugs that reduce blood pressure angiotensionconverting enzyme inhibitors improve diabetic control.

Surgical management can be considered in people with type1 diabetes that is pancreas transplant [40].Inpatients with morbid obesity weight loss surgery can be done [41].

HYPERURICEMIA

Hyperuricemia has gained importance as many studies have reported that it not only has an important role in the development of metabolic disease but also microvascular risk factors 42-45. Uric acid is primarily a purine metabolic waste product.About 70% of it gets excreted by the kidneys. Hence decreased excretion of the uricacid is an important cause of hyperuricemia[46].

Few studies have reported that the prevalence of hyperuricemia was associated with BMI and waist circumference [47,48, 49] associated with increasedleptin production and insulin resistance [50, 51] and both inversely correlated with renal clearance of urate.

Nan et al reported that serum uric acid level decreased with increase of glucose level in patients with diabetes. Both glycemic control and function of beta cell decrease with increased duration of diabetes. Hyperfilteration by glomeruli caused by hyperglycemic state increases the excretion of uricacid. This may partly explain the inverse relationship between serum uricacid and diabetes [52]

Serum uric acid levels are determined by a balance between uricacid production and excretion. There is no method for detecting the uric acid production in humans. Uric acid production is indirectly calculated through serum Uric acid level and urine excretion. The rate limiting step of uric acid production is an enzymatic reaction of the xanthine dehydrogenase/ xanthine oxidase enzyme that oxidises hypoxanthine – xanthine into uric acid. It is absorbed in the liver and small intestine and it is the major source of uric acid [53]. The enzyme is also produced in adipose tissue, vascular endothelium and macrophages all of which are involved in life style related diseases [54].

The kidney is an important regulator of circulating uric acid and is responsible for 60-70 % of total body uric acid excretion [55]. The remaining uric acid is secreted into the intestine followed by bacterial uricolysis[55]. Uric acid excretion includes uratesecretion and re-absorption. An earlier study suggests the involvement of hyper filtration[56]. During the secretion process, uric acid is transported into proximal tubular cells via OAT 1/3 and / or NADC3 and then secreted by HUA transporter sodium phosphate co transporter, ATP binding cassette. 90% of uric acid filtered is reabsorbed [55].

Uric acid level in diabetes:

Table 1 Association between life-style related diseases and uric acid metabolism

Diseases/status	SUA level	UA production	Focus 1	UA excretion	Focus 2
T1DM	High/low				
Glucosuria	Low			Up	Glomerulus
Insulin resistance	High			Down	Proximal tubule cell
Use of SGLT2 inhibitor	Low			Up	
Retinopathy		Up	Vitreus		
MetS	High	Up	Adipocyte/liver?	Down	Proximal tubule cell
CKD	High	Up	Vascular endothelial cell/inflammatory cell	Down/up	Kidney/intestine
Hypertension	High	Up			
Atherosclerosis		Up	Vascular endothelial cell/inflammatory cell		
Reperfusion injury		Up	Vascular endothelial cell		
Heart failure		Up	Inflammatory cell		
Fructose intake	High	Up	Liver	Down	
Sodium intake	High			Down	
Thiazide administration	High			Down	Proximal tubule cell

The above table shows association between lifestyle and uric acid metabolism [56 -64.] Some diseases raise serum uric acid level and uric acid affects the disease progression in others.

In patients with diabetes, serum uric acid is low as there is increased urate clearance [66]. In these patients hypourecemia is associated with glycosuria [67]. Elevated serum uric acid is a feature of hyperinsulinemia or insulin resistance [68.] Type II diabetes mellitus is a risk factor for cholelithiasis and is associated with uric acid stones. New class of antidiabetic agents sodium glucose co-transporter 2 inhibitor lowers uric acid through altering of uric acid transport activity in renal tubule by increasing glycosuria [69- 70.]

Besides age, race, family, history of diabetes, glucose intolerance – serum uric acid has been suggested to be associated with complications of diabetes [71]. Elevated serum uric acid plays an important role in Type II DM and its complications. Diabetogenic action of uric acid was reported in 1950 [(72).] The mechanism of this is unknown. Serum uric acid affects insulin resistence[73]. In summary a link between serum uric acid and insulin resistance has repeatedly been shown and uric acid itself plays an important role in exacerbation of insulin resistance [74.]

DIABETIC COMPLICATIONS AND URIC ACID LEVELS:

Development of vascular complications were predicted independently by serum uric acid [75]. We have discussed the relation between serum uric acid and each diabetic complication below.

Diabetic Neuropathy:

Diabetic neuropathy is a complication of the disease[76]. It causes chronic numbness, loss of quality of life and pain. The prevalence of diabetic neuropathy is associated with a significant increase of uric acid levels [77.]

Several studies show that when controlled for factors such as age, gender, BMI and renal function, serum uric acid was high in patients with diabetic neuropathy [78 -80].

The pathophysiology of diabetic neuropathy is not completely understood, there are multiple metabolic imbalance underlying in the development of diabetic neuropathy [81.]

Few risk factors for neuropathy are hyperglycemia, dyslipidemia and cardiovascular dysfunction. The polyol pathway, non-enzymaticglycation, oxidative stress are believed to be causative factors. Oxidative stress and inflammation are involved in XDH/ XO activity. Therefore understood that uric acid generation by XDH/ XO play a role in diabetic neuropathy.

Diabetic Retinopathy:

Diabetic retinopathy is an accumulation of visceral fat and insulin resistance in diabetic patient [82.] Earlier reports stated no significant difference in uricacid levels in patients with or without diabetic retinopathy [83].

Recent studies show significant increase of uric acid level in diabetic retinopathy patients. Serum uricacid is shown to be associated with severity of retinopathy. COX – regression analysis showed that patients with serum uricacid levels in the third and fourth quartiles had increased serum uric acid levels compared to that in the first quartile [84.] Vitreous uricacid and glucose concentration were higher in proliferative diabetic retinopathy than in NPDR. Focal and uric acid production in vitreous is believed to be involved in pathogenesis and progression of diabetic retinopathy [85.]

Diabetic Nephropathy:

Shichiri et al [86] proved that glomerular hyperfiltration occurs in non-insulin diabetes mellitus and that it lowers serum uricacid levels by increasing the renal clearance of urate[86.]

Other reports imply that high uricacid levels define the prognosis of diabetic nephropathy [87]. Serum uric acid is also associated with CKD[88.]

Serum uricacid is associated with disease progression in early stage of nephropathy [89.] Serum uricacid concentration more than 6.3 mg/dl carries a poor prognosis in a diabetic patient with nephropathy. Few data show association between uric acid and disease progression is

independent of diabetic control in a multivariate analysis. The progression and regression of urinary albumin excretion was not associated with uric acid levels [90]. Uric acid is an independent risk factor for renal dysfunction after adjustment for confounding factors.

Uricacid is reduced in a diabetic patient due to hyperfiltration[91]. But reduced uricacid excretion during renal dysfunction increases serum uricacid levels. There is data that suggest higher level of uric acid production is also involved in pathophysiology of neuropathy progression.

Severalrecent studies are under way to delay nephropathy progression [92 -94]. Allopurinol significantly reduces serum uric-acid levels in hyperuricemic patients with diabetic complications.

Diabetic foot:

There are a few reports regarding the relationship between diabetic foot and uric acid levels. One study states that elevated uric acid levels anindependent risk factor for diabetic foot in diabetic patient [95].

Significance of future uric acid metabolism research for the treatment of patients with diabetes:

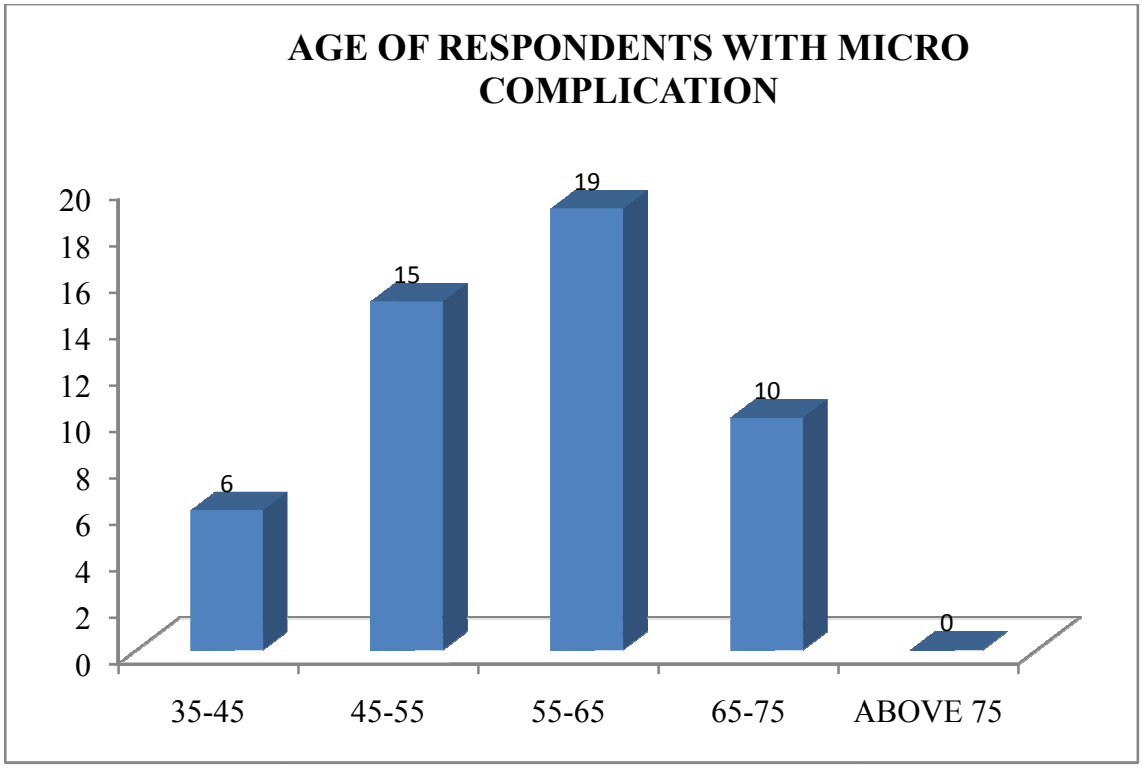
Xanthine dehydrogenase/xanthine oxidase has been studied for many years and allopurinol was used before enzyme inhibition therapy was found. This progress in research is related to the global demand to target lifestyle related disease such as diabetes. These researches have led to development of new powerful uric acid lowering agents.

RESULTS

ANALYSIS AND INTERPRETATION

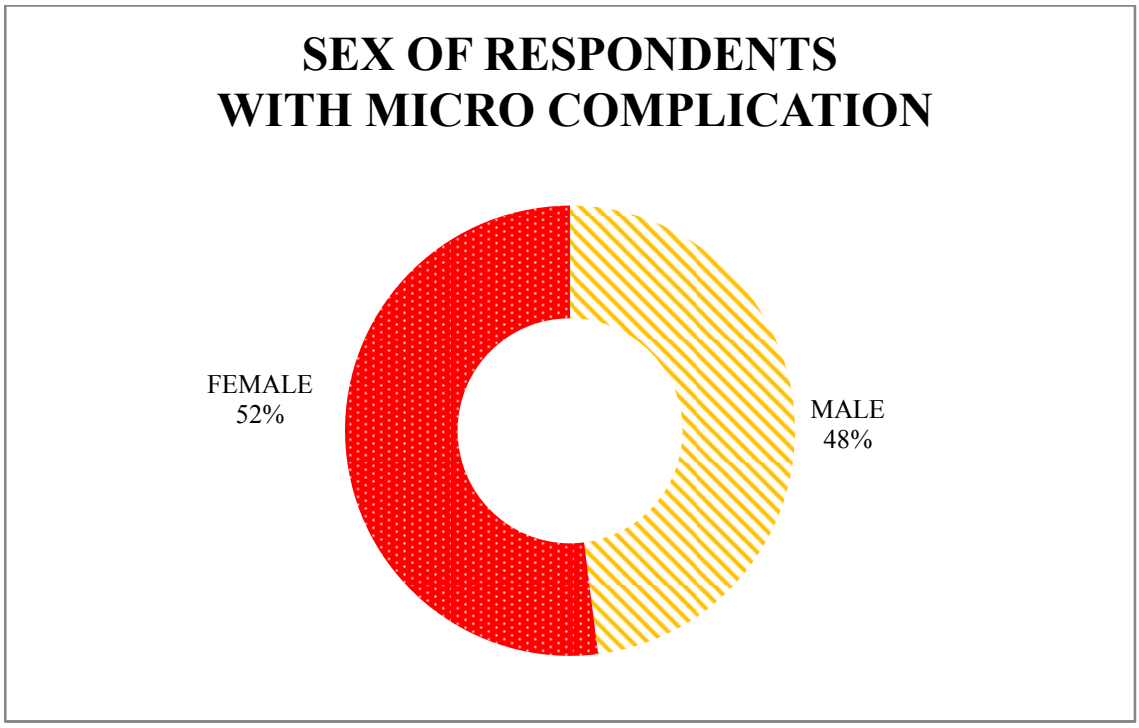
FREQUENCY DISTRIBUTION OF AGE (MICRO COMPLICATION)

S.NO	AGE	FREQUENCY	PERCENTAGE
1	35 years – 44 years	6	12%
2	45 years -54 years	15	30%
3	55 years -64 years	19	38%
4	65 years -74 years	10	20%
5	ABOVE 75 years	-	-
	TOTAL	50	100



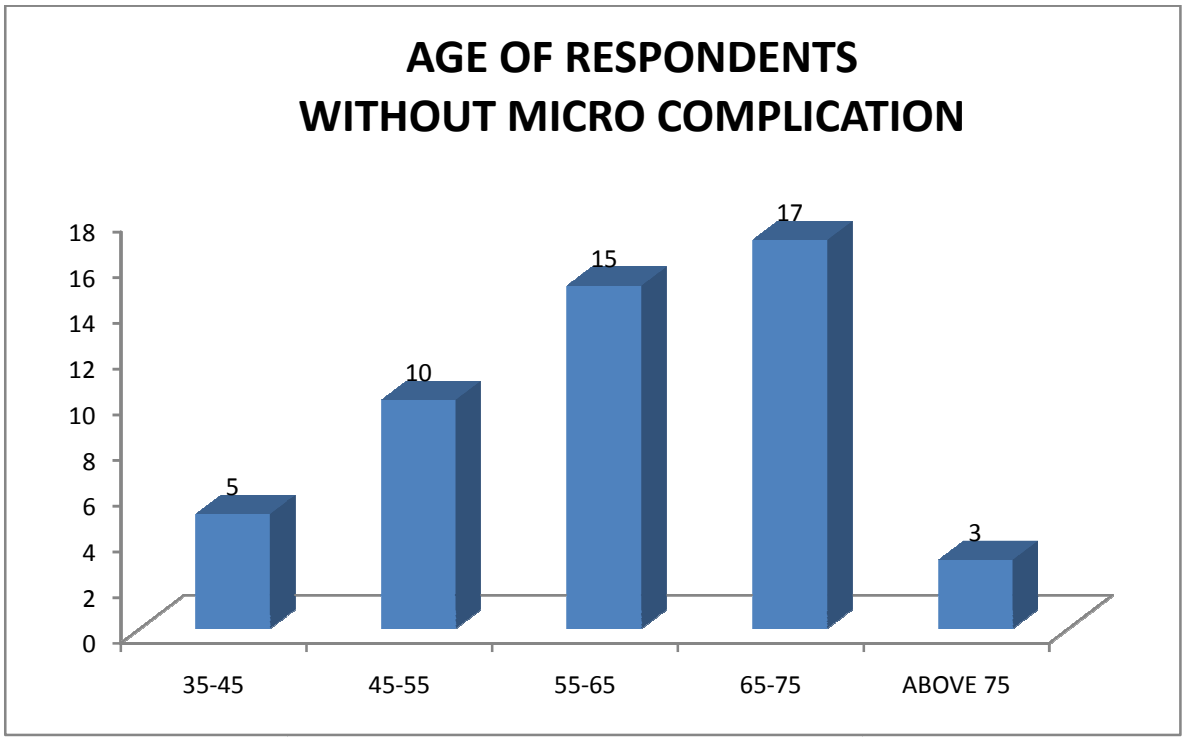
FREQUENCY DISTRIBUTION OF SEX (MICRO COMPLICATION)

S.NO	AGE	FREQUENCY	PERCENTAGE
1	MALE	24	48%
2	FEMALE	26	52%
	TOTAL	50	100



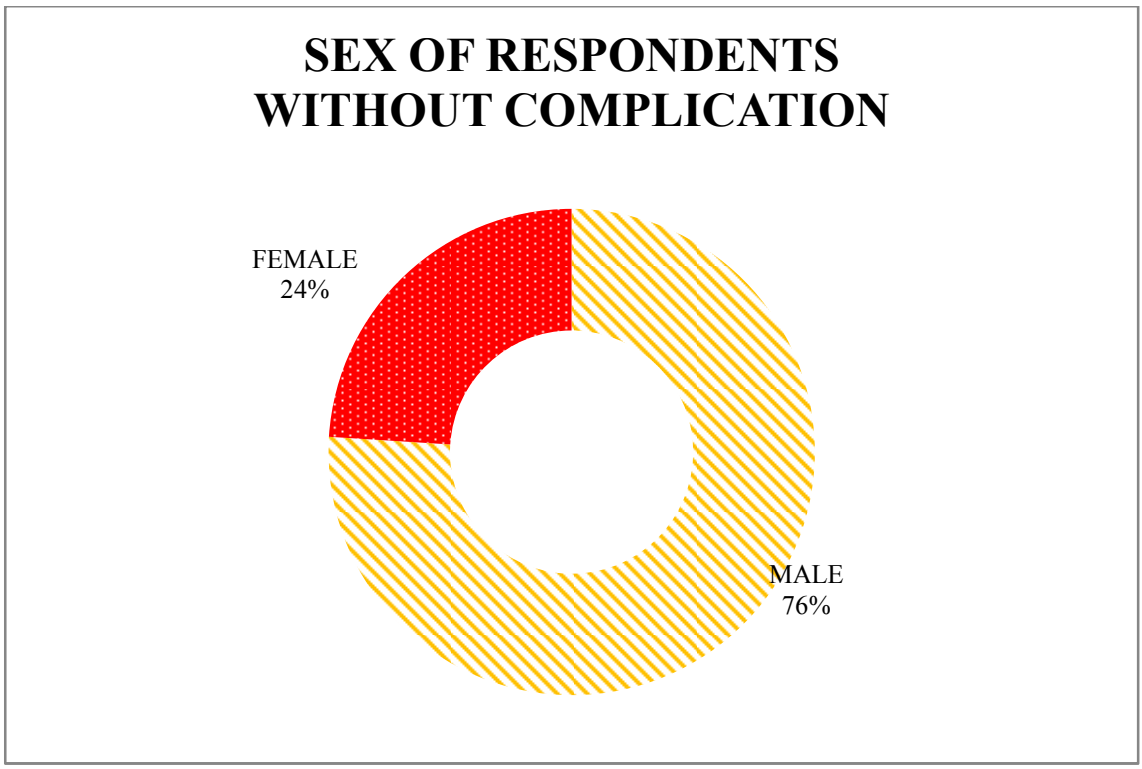
FREQUENCY DISTRIBUTION OF AGE
(WITHOUT MICRO COMPLICATION)

S.NO	AGE	FREQUENCY	PERCENTAGE
1	35 years – 45 years	5	10%
2	45 years -55 years	10	20%
3	55 years -65 years	15	30%
4	65 years -75 years	17	34%
5	ABOVE 75 years	3	6%
	TOTAL	50	100



FREQUENCY DISTRIBUTION OF SEX (WITHOUT MICRO COMPLICATION)

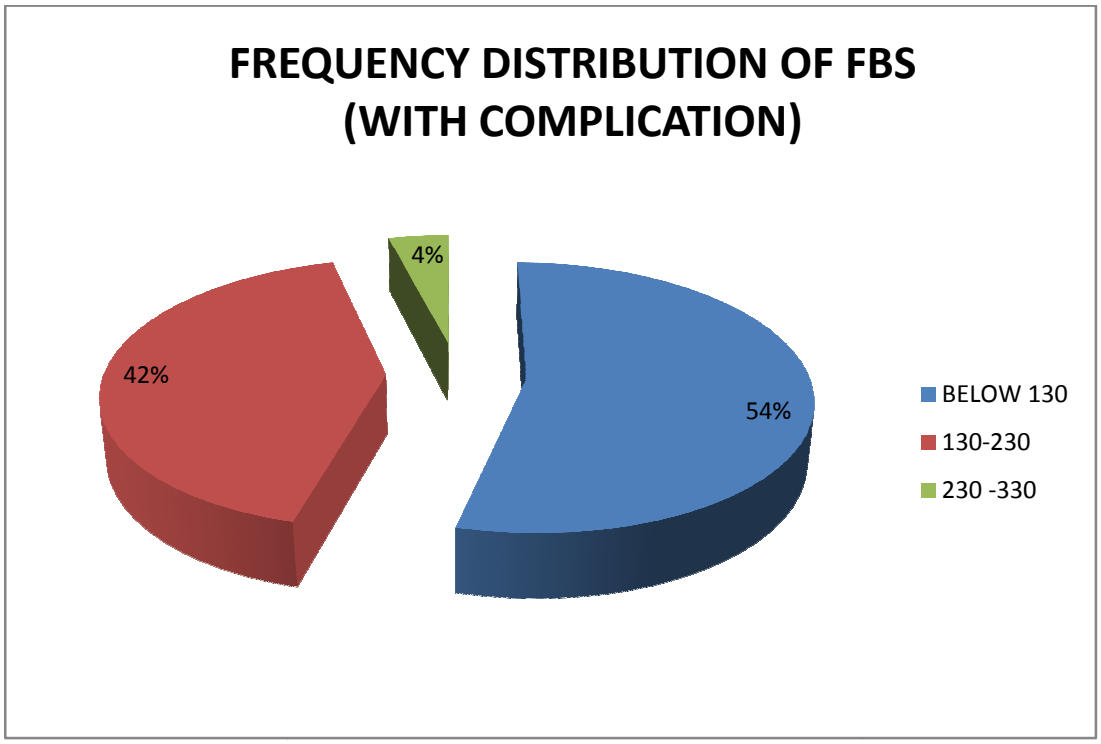
S.NO	AGE	FREQUENCY	PERCENTAGE
1	MALE	38	76%
2	FEMALE	12	24%
	TOTAL	50	100



FREQUENCY DISTRIBUTION OF FBS (MICRO COMPLICATION)

S.NO	FBS	FREQUENCY	PERCENTAGE
1	BELOW 130	27	54%
2	130-230	21	42%
3	230 -330	2	4%
	TOTAL	50	100

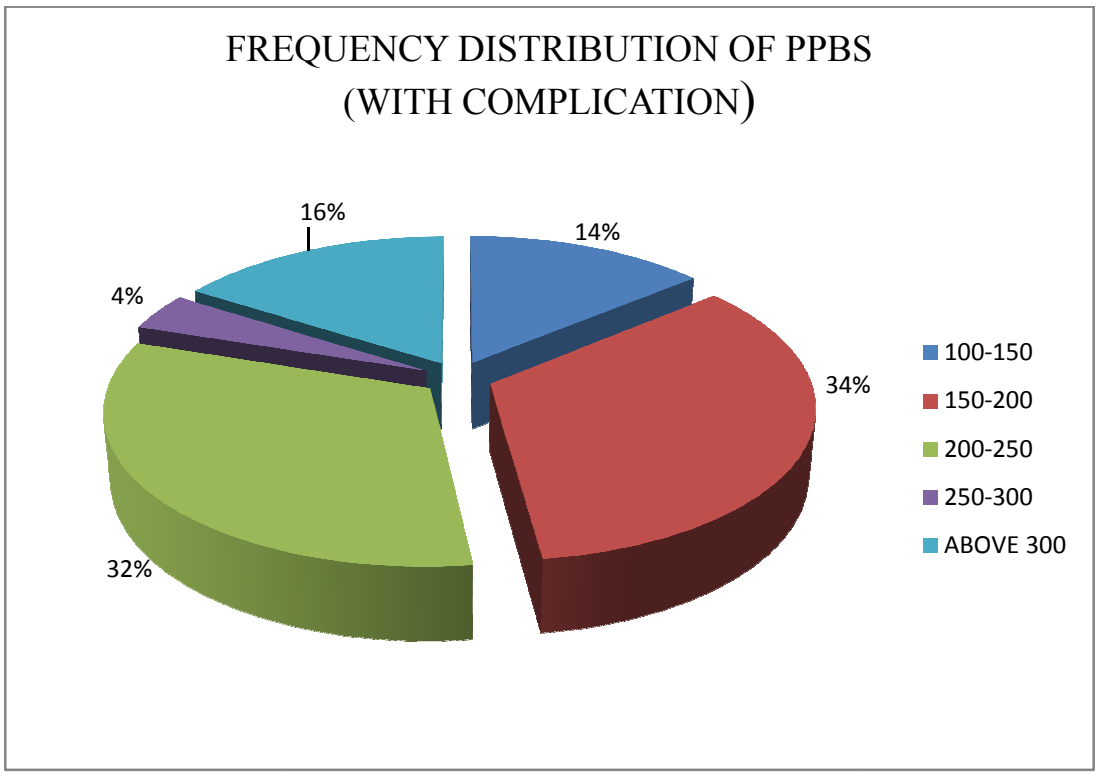
From the above table, 54% of respondents have FBS below 130, 42% are under the category of 130-230 and 4% under 230-300.



FREQUENCY DISTRIBUTION OF PPBS (MICRO COMPLICATION)

S.NO	PPBS	FREQUENCY	PERCENTAGE
1	100-150	7	14%
2	150-200	17	34%
3	200-250	16	32%
4	250-300	2	4%
5	ABOVE 300	8	16%
	TOTAL	50	100

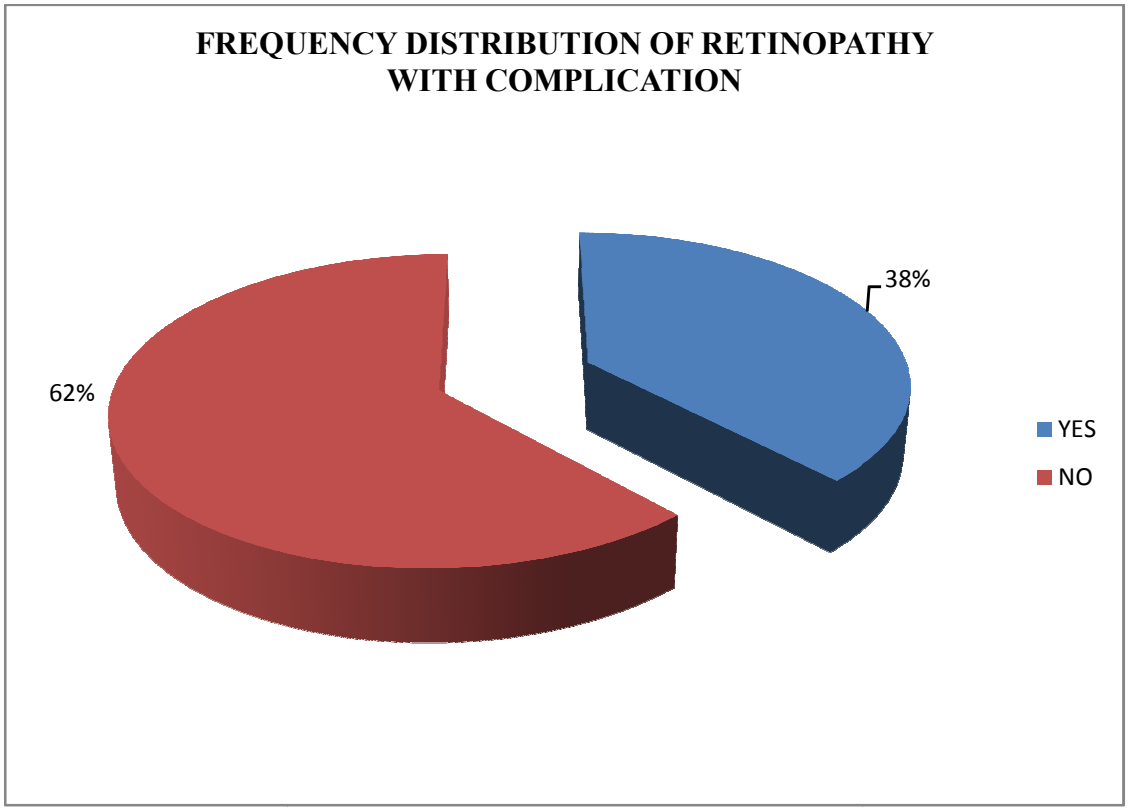
From the above table, 34% of respondents have PPBS ranges 150-200, 32% are under the category of 200-250 and 16% above 300.



FREQUENCY DISTRIBUTION OF RETINOPATHY (MICRO COMPLICATION)

S.NO	RETINO	FREQUENCY	PERCENTAGE
1	YES	19	38%
2	NO	31	62%
	TOTAL	50	100

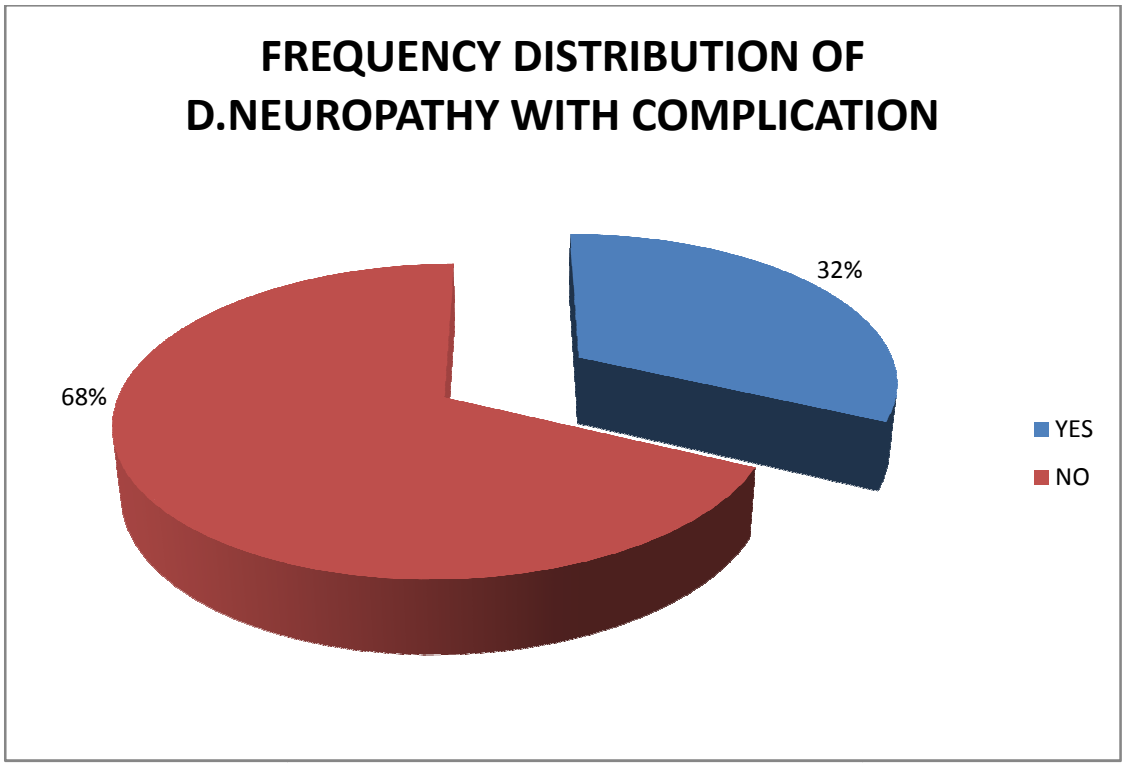
From the above table, 62% of respondents have no Retinopathy Complication and 38% have DR



FREQUENCY DISTRIBUTION OF NEUROPATHY (MICRO COMPLICATION)

S.NO	NEUROPATHY	FREQUENCY	PERCENTAGE
1	YES	16	32%
2	NO	34	68%
	TOTAL	50	100

From the above table, 68% of respondents have no Neuropathy Complication and 32% have Neuropathy

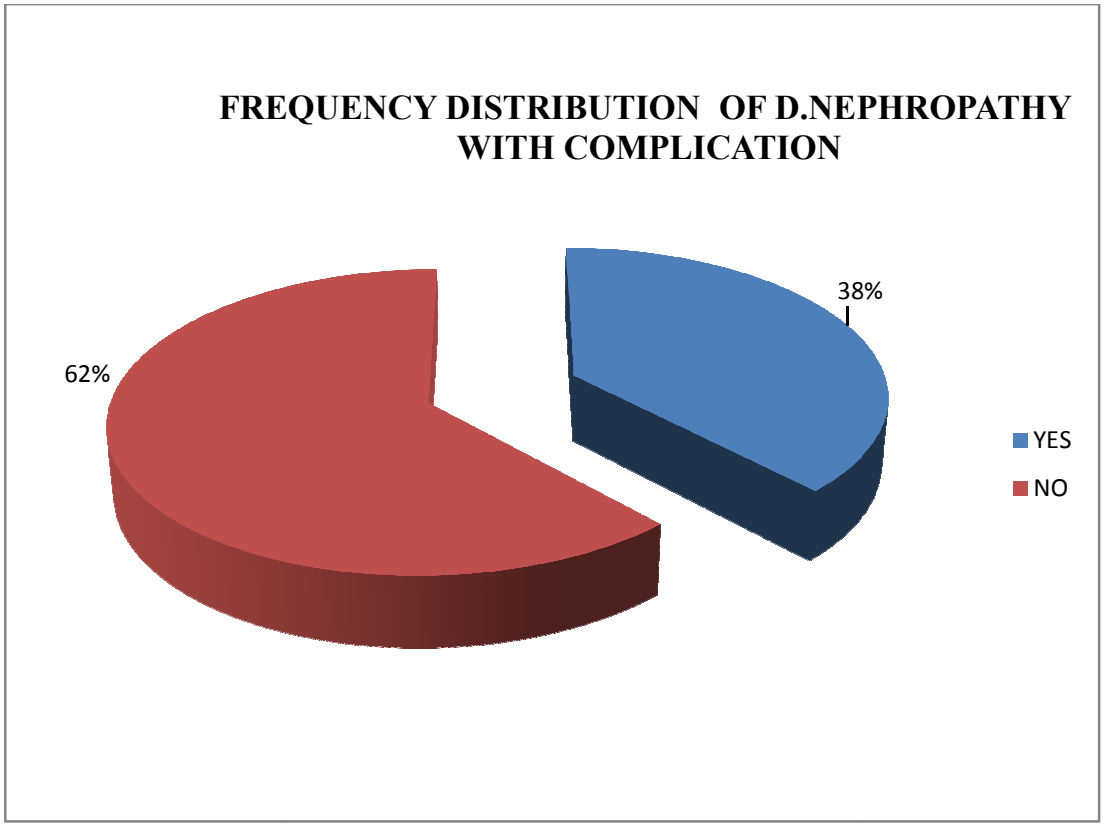


FREQUENCY DISTRIBUTION OF NEPHROPATHY (MICRO COMPLICATION)

S.NO	NEPHROPATHY	FREQUENCY	PERCENTAGE
1	YES	19	38%
2	NO	31	62%
	TOTAL	50	100

From the above table, 62% of respondents have no Nephropathy

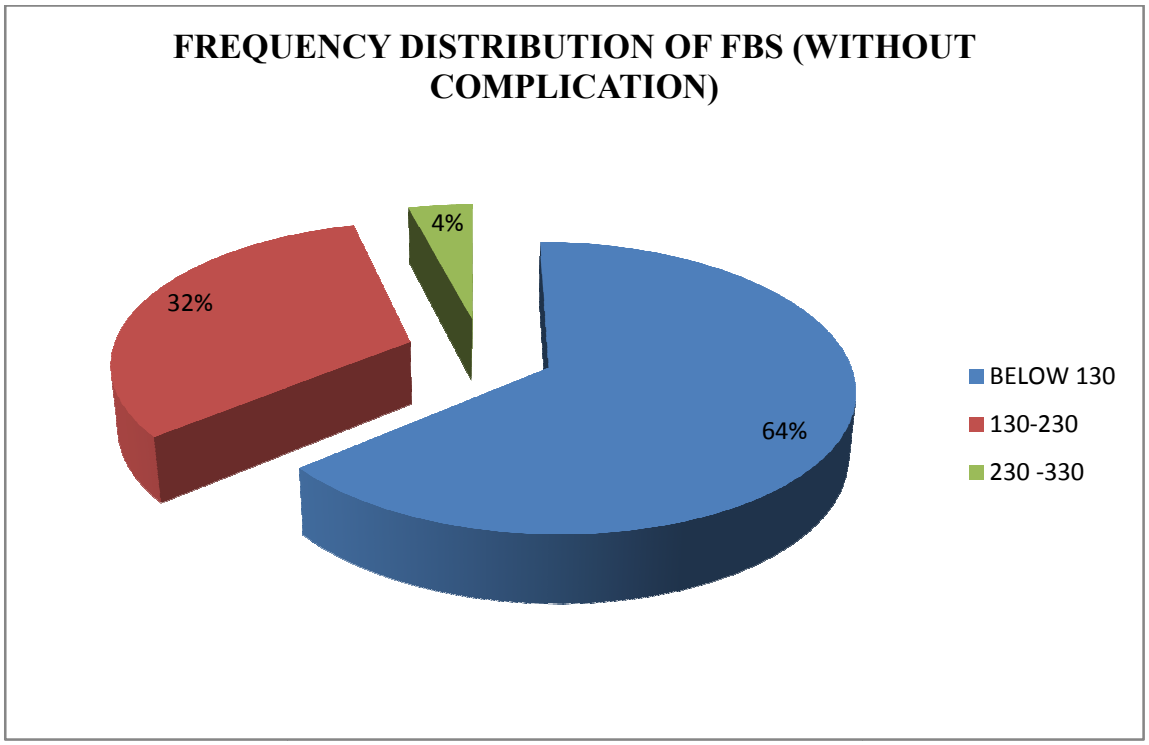
Complication and 38% have Neuropathy



FREQUENCY DISTRIBUTION OF FBS (WITHOUT MICRO COMPLICATION)

S.NO	FBS mg/dL	FREQUENCY	PERCENTAGE
1	BELOW 130	32	64%
2	130-230	16	32%
3	230 -330	2	4%
	TOTAL	50	100

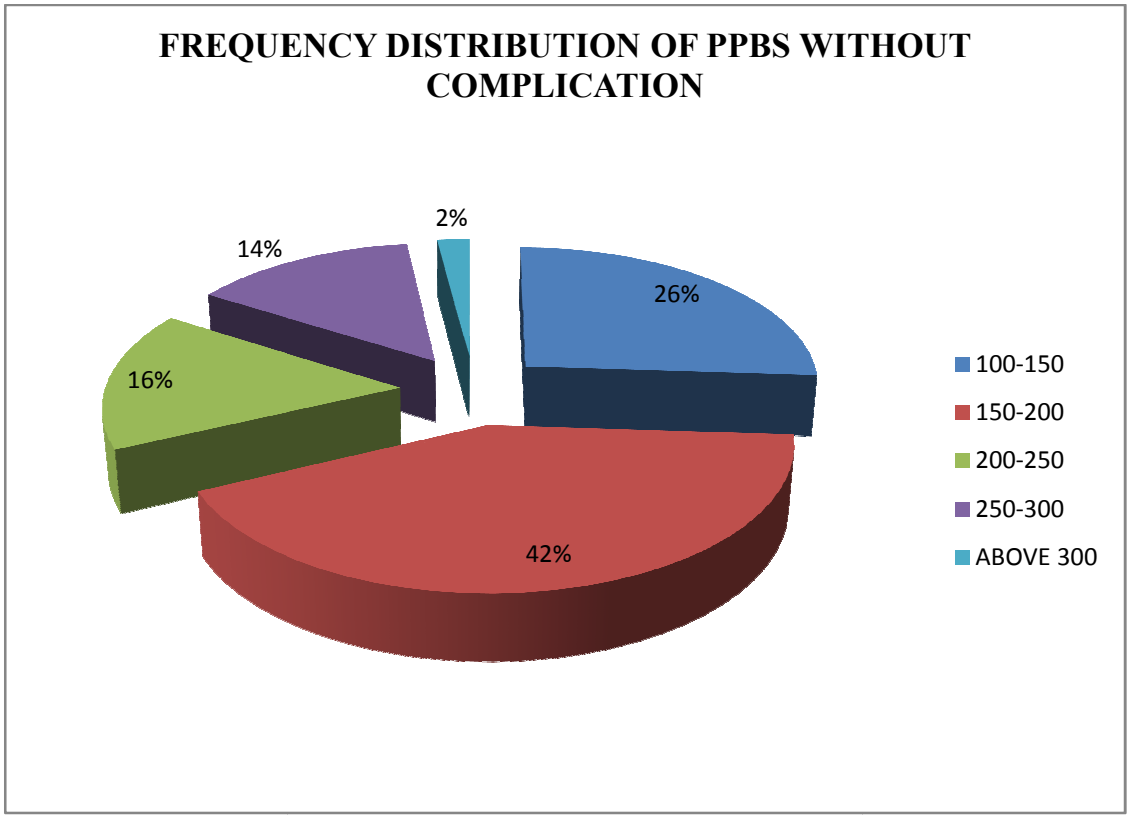
From the above table, 64% of respondents have FBS below 130, 32% are in the category of 130-230 and 4% have 230-300.



FREQUENCY DISTRIBUTION OF PPBS (WITHOUT MICRO COMPLICATION)

S.NO	PPBS mg/dL	FREQUENCY	PERCENTAGE
1	100-150	13	26%
2	150-200	21	42%
3	200-250	8	16%
4	250-300	7	14%
5	ABOVE 300	1	2%
	TOTAL	50	100

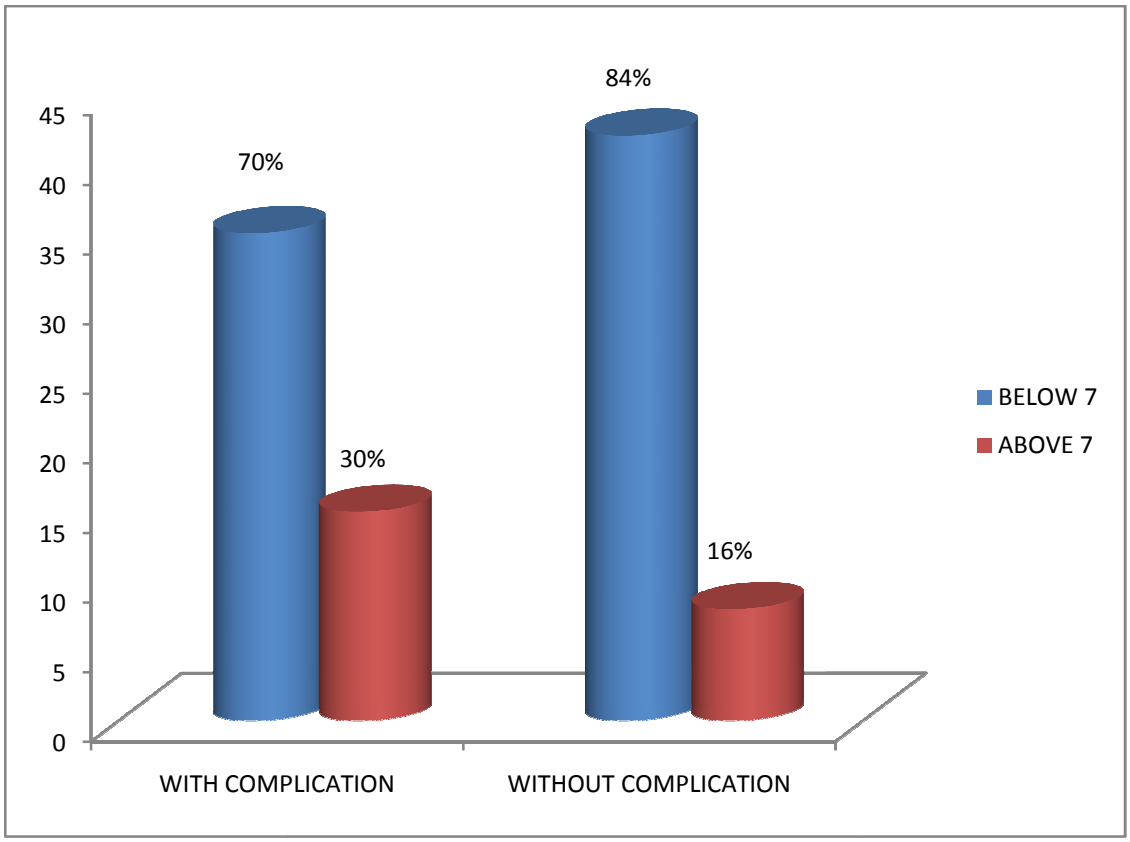
From the above table, 42% of respondents have PPBS ranges 150-200, 26% in the category of 100-150 and 16% above 250-250.



FREQUENCY DISTRIBUTION OF URIC ACID (WITH COMPLICATION AND WITHOUT COMPLICATION)

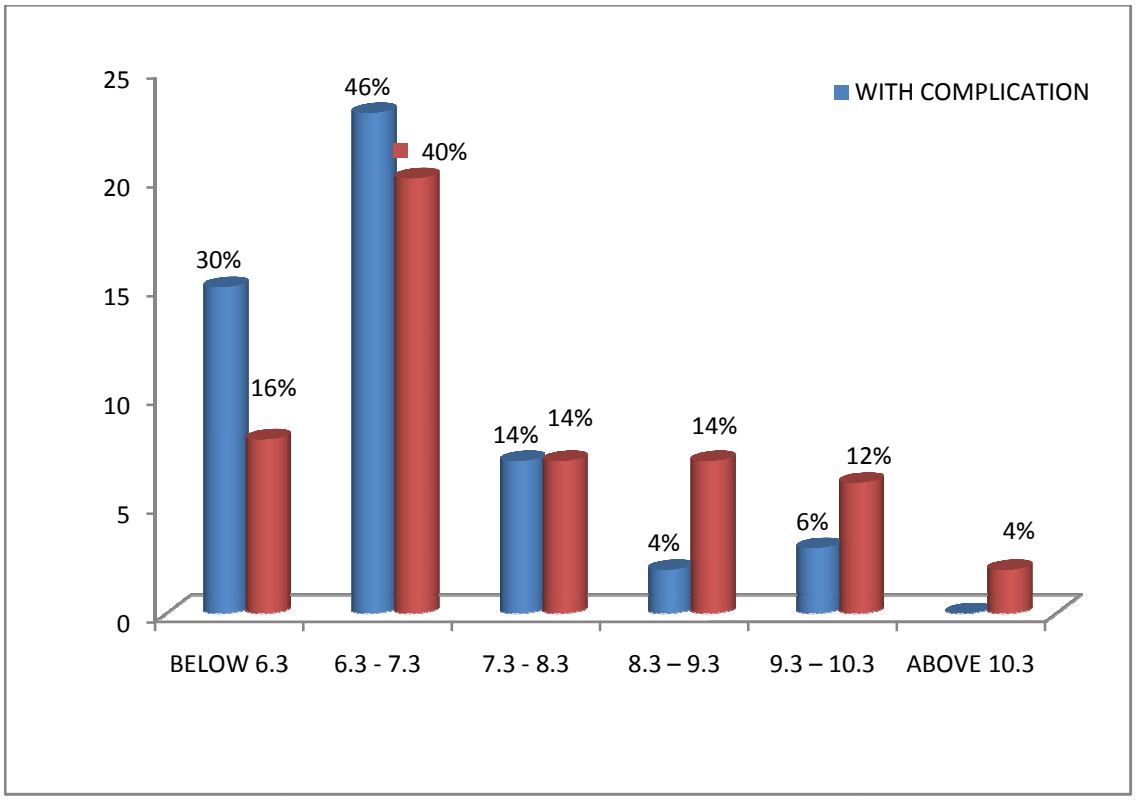
S NO	URIC ACID LEVEL	With Complication	%	Without Complication	%
1	BELOW 7	35	70%	42	84%
2	ABOVE 7	15	30%	8	16%
	TOTAL	50	100	50	100

Above table reveals, that Hyperuricemia(Uric acid above 7**) is twice as elevated in the Micro Complication group (30%)** when compared with no micro complication group (15%)



FREQUENCY DISTRIBUTION HbA1C
(WITH COMPLICATION AND WITHOUT COMPLICATION)

SNO	HbA1C	WITH COMPLICATION		WITHOUT COMPLICATION	
		NO.OF PATIENTS	%	NO.OF PATIENTS	%
1	BELOW 6.3	15	30%	8	16%
2	6.3 – 7.3	23	46%	20	40%
3	7.3 - 8.3	7	14%	7	14%
4	8.3 – 9.3	2	4%	7	14%
5	9.3 – 10.3	3	6%	6	12%
6	ABOVE 10.3	-	-	2	4%
	TOTAL	50		50	



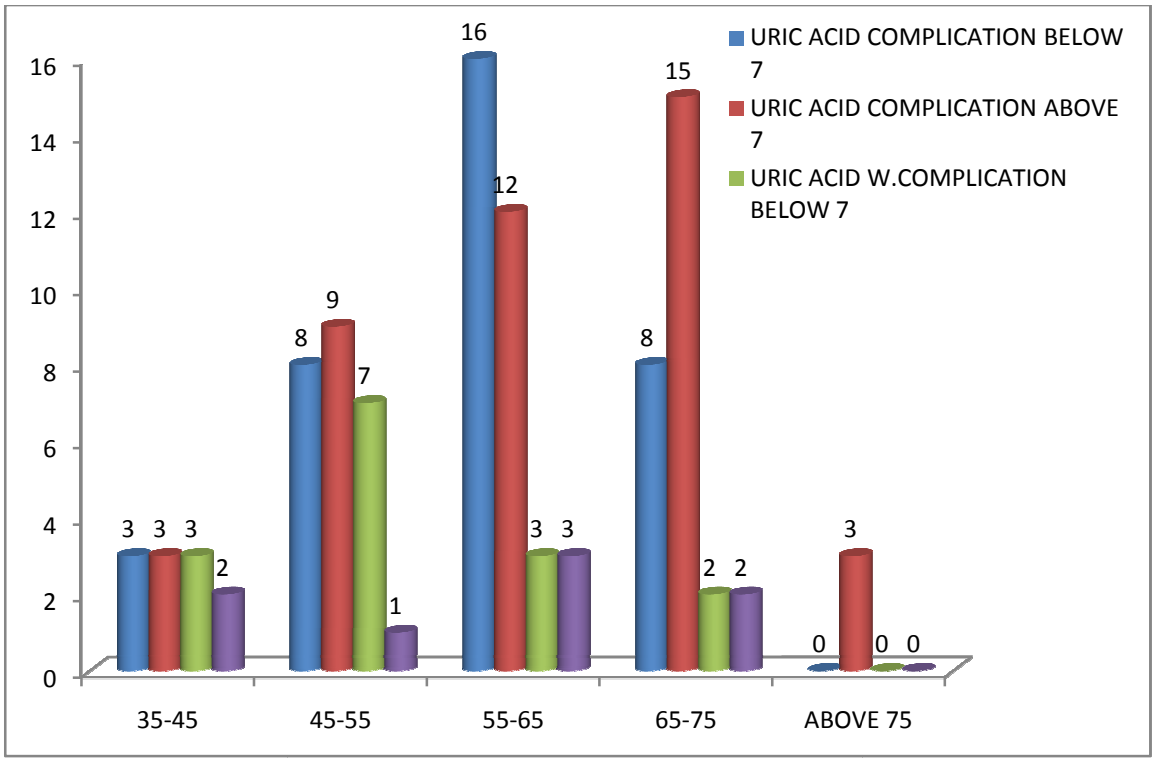
AGE AND URIC ACID LEVEL
(WITH COMPLICATION AND WITHOUT COMPLICATION)

S. No	Age	URIC ACID							
		With complication				Without complication			
		Below 7	%	Above 7	%	Below 7	%	Above 7	%
1	35-45	3	8.57%	3	20%	3	7.14%	2	25%
2	45-55	8	22.85%	7	46.7%	9	21.42%	1	12.5%
3	55-65	16	45.71%	3	20%	12	28.57%	3	37.5%
4	65-72	8	22.85%	2	13.3%	15	35.71%	2	25%
5	Above 75	-	-	-		3	7.14%	-	-
	TOTAL	35	100%	15	100%	42	100%	8	100%

Above table reveals, **Uric acid is elevated in the group with microvascular complication** in the age group**45 – 55 (46.7%)**

Without complications below 7

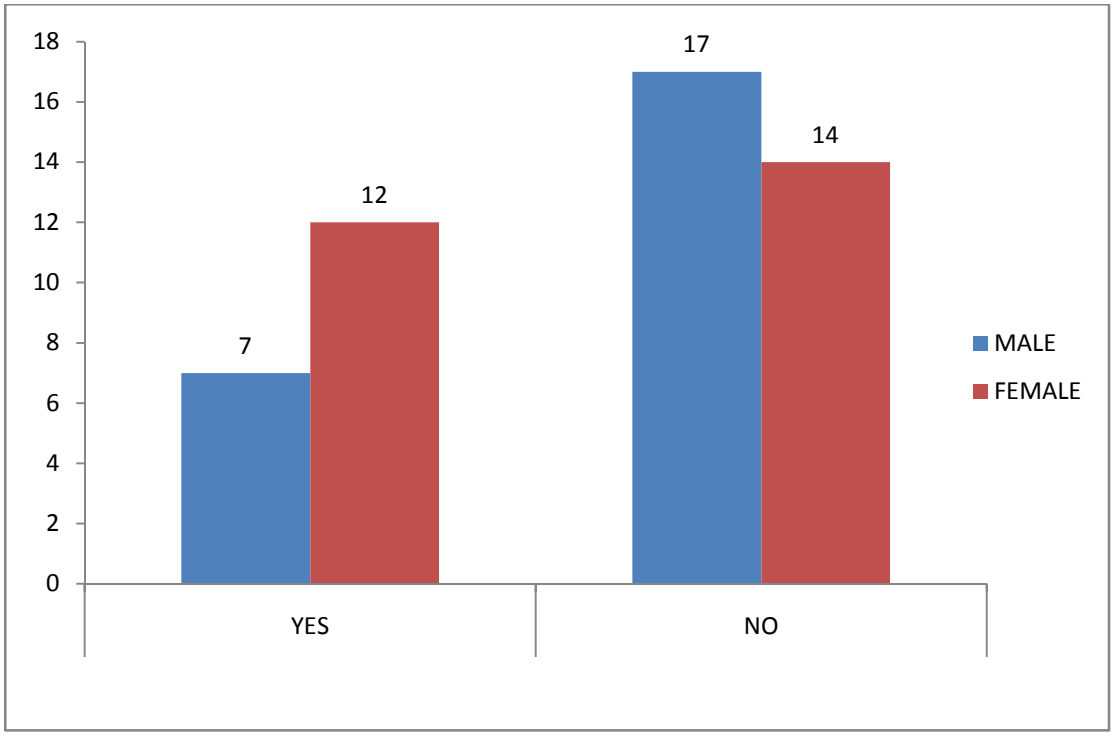
Without complications above 7



FREQUENCY DISTRIBUTION OF AGE AND RETINOPATHY

S.NO	SEX	RETINOPATHY		TOTAL
		YES	NO	
1	MALE	7	17	24
2	FEMALE	12	14	26
	TOTAL	19	31	50

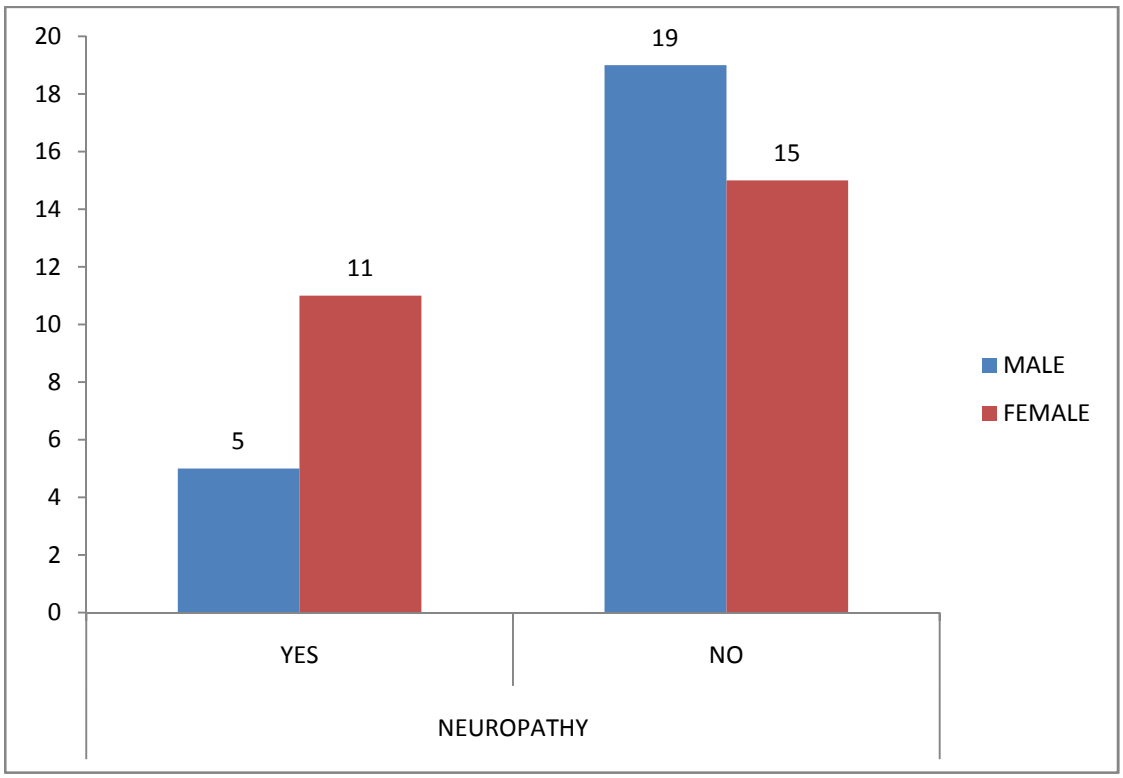
The Above table reveals that Retinopathy complication is more in female (12 patients) than in Male.



FREQUENCY DISTRIBUTION OF AGE AND NEUROPATHY

S.NO	SEX	NEUROPATHY		TOTAL
		YES	NO	
1	MALE	5	19	24
2	FEMALE	11	15	26
	TOTAL	16	34	50

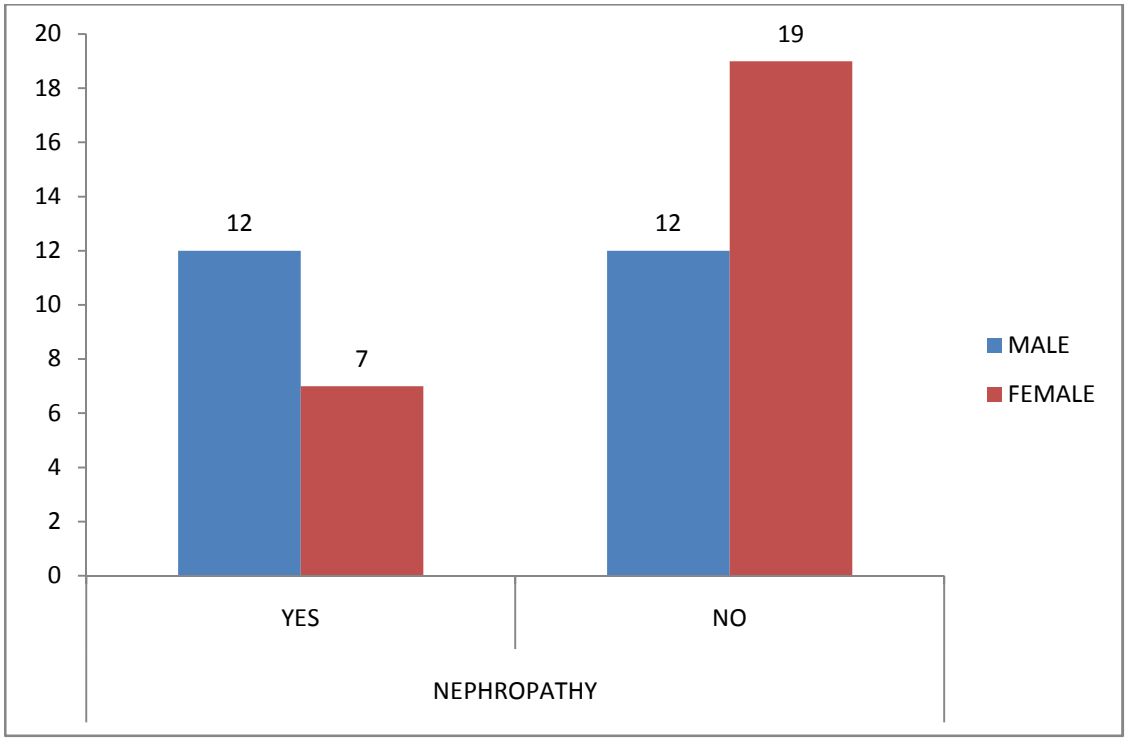
The Above table reveals that Neuropathy complication is more in female (11 patients) than in Male.

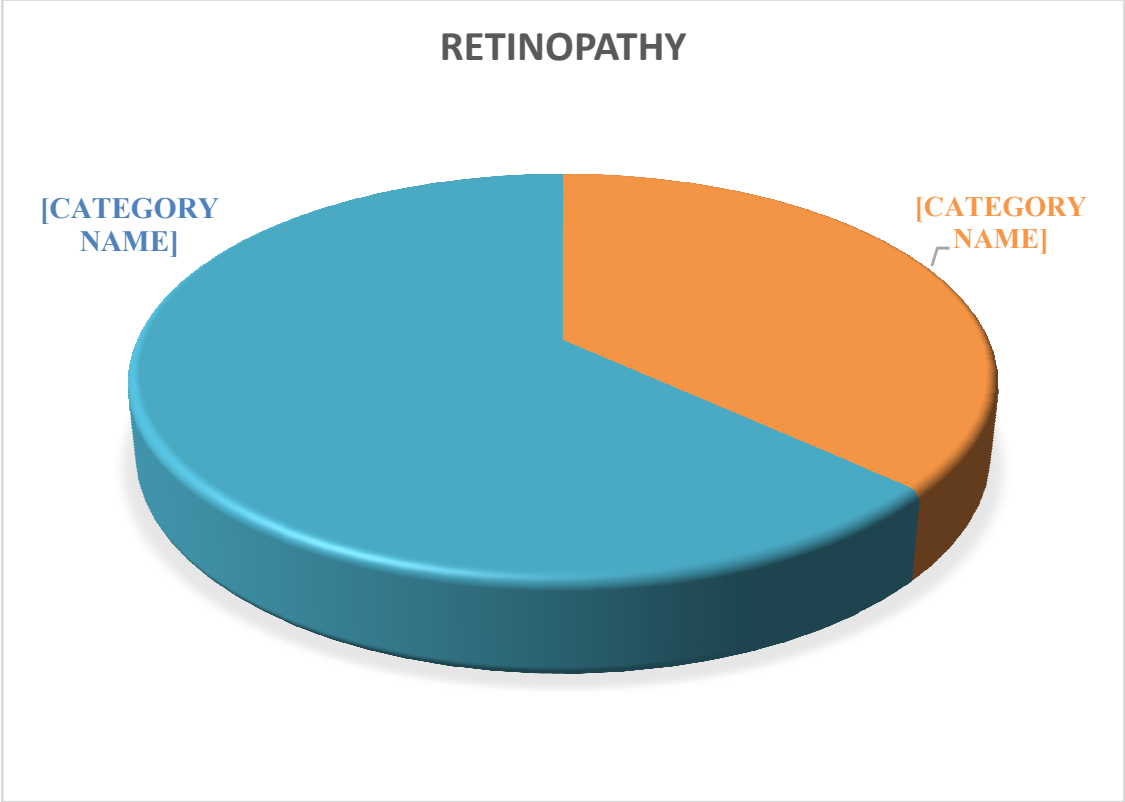


FREQUENCY DISTRIBUTION OF AGE AND NEPHROPATHY

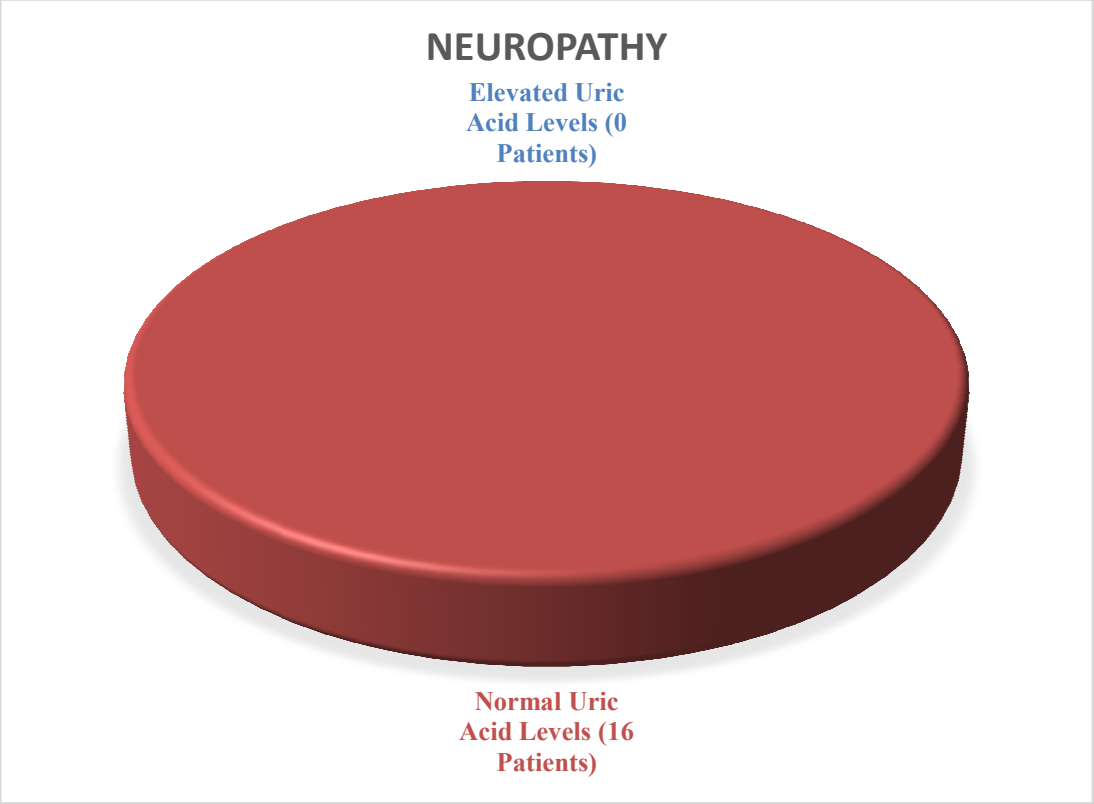
S.NO	SEX	NEPHROPATHY		TOTAL
		YES	NO	
1	MALE	12	12	24
2	FEMALE	7	19	26
	TOTAL	19	31	50

The Above table reveals that Nephropathy complication is more in male (12 patients) than in Female.

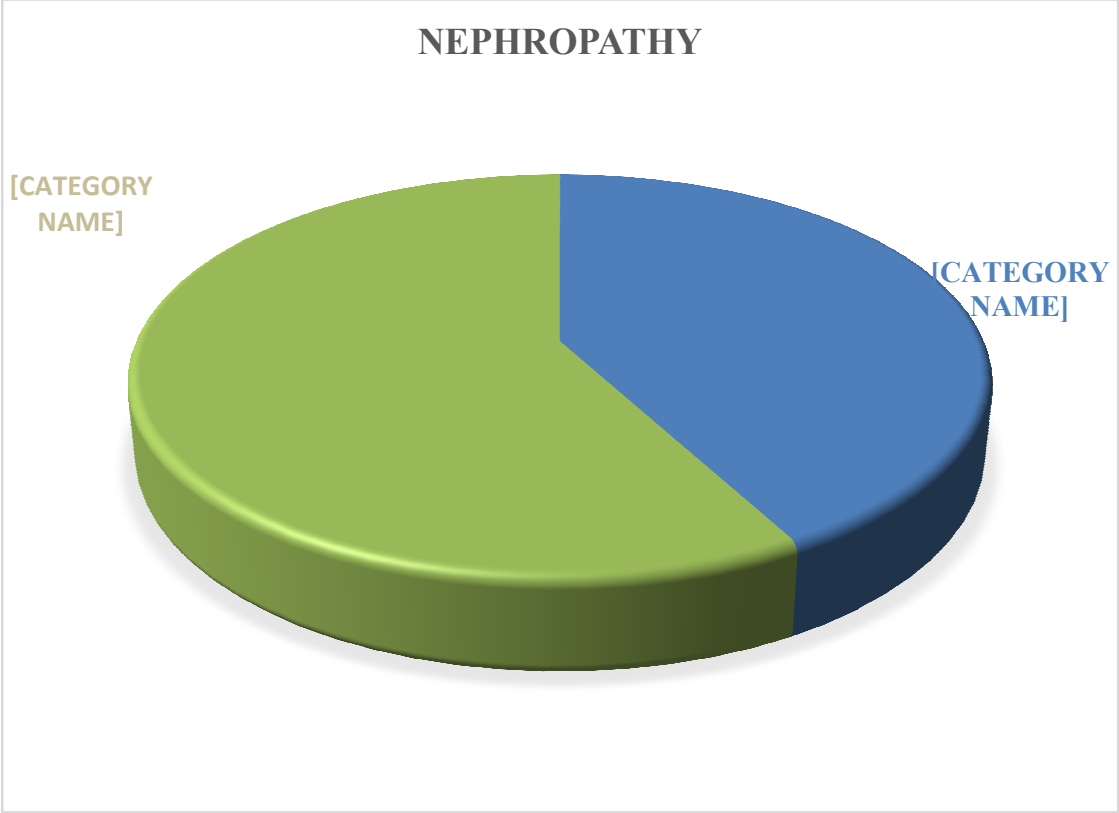




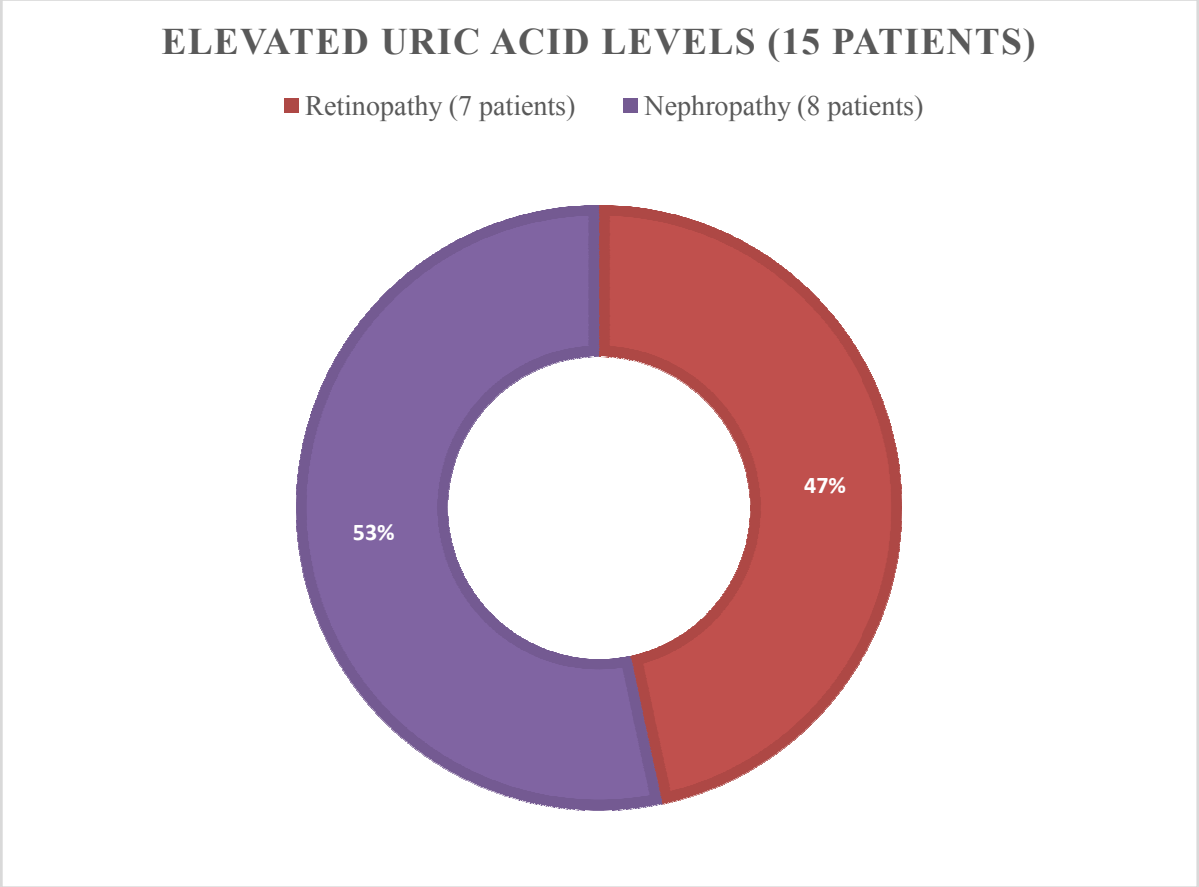
Out of the 19 patients with diabetic retinopathy, 7 patients had elevated serum uric acid levels.



Out of the 16 patients with diabetic neuropathy, none had hyperuricemia.



Out of the 19 patients with Diabetic Nephropathy, 8 patients had elevated serum uric acid levels.



In our study, in the group of 50 patients with microvascular complications, 15 patients had elevated serum uric acid levels, out of which, 7 patients had retinopathy and 8 patients had nephropathy.

CHI-SQUARE TEST (HYPERURICEMIA AND RETINOPATHY)

Null hypothesis: There is no association between Uric acid and Retinopathy

H_0: Uric acid and retinopathy are independent

H_1: Uric acid and retinopathy are not independent

	Value	Df	Asymp. Sig (2 sided)
Pearson chi-square	.683[a]	1	0.409
Likelihood Ratio	.675	1	.411
N. of Valid cases	50		

Pearson chi-square value is .683with degree of freedom of 1. The significant value is 0.409(i.e. P value). Since P value is greater than 0.05, the difference between observed value and expected value is not significant. Therefore Null hypothesis is accepted. **Thus there is no association between hyperuricemia and Retinopathy.**

CHI-SQUARE TEST (HYPERURICEMIA AND NEPHROPATHY)

Null hypothesis: There is no association between Uric acid and Nephropathy

H_0: Uric acid and Nephropathy are independent

H_1: Uric acid and Nephropathy are not independent

	Value	Df	Asymp. Sig (2 sided)
Pearson chi-square	2.138[a]	1	0.144
Likelihood Ratio	2.105	1	0.147
N. of Valid cases	50		

Pearson chi-square value is 2.138 with degree of freedom of 1. The significant value is 0.144(i.e. P value). Since P value is greater than 0.05, the difference between observed value and expected value is not significant. Therefore Null hypothesis is accepted. **Thus there is no association between hyperuricemia and Nephropathy.**

Inference: Uric acid is elevated in microvascular complication group when compared to no Complication group. **Hyperuricemia is not independently associated with** Nephropathy and Retinopathy and neuropathy.**But uric acid is elevated in the microvascular complication group when taken as a whole.**

DISCUSSION

Diabetes Mellitus was one of the earliest diseases portrayed (1) in an Egyptian Manuscript from around 1500 BC, the first described case being type 1 DM. (2)Diabetes is caused either due to insufficient production of insulin by the pancreatic islets or due to peripheral receptor level resistance to insulin despite adequate circulating insulin levels (4).

Increasing amounts of uric acid in the serum causes Gout and this is one of the most significant features oflifestyle-relateddisorder.Uric acid is primarily a purine metabolic waste protect about 70% of it gets excreted in the kidneys. Hence decreased excretion of uric-acid is an important cause of hyper-uricemia[46]. There is no method for detecting the uric acid production in humans. Uric acid production is indirectly estimated through serum Uric acid level and urine excretion.

Development of vascular complications were predicted independently by serum uric acid [75].

In a study conducted by Agrawal et al. it was concluded that the Uric acid levels are raised in patients with diabetes.They found lower levels of uric acid in diabetic subjects compared to healthy controls but higher level of uric acid in subjects of diabetes with retinopathy. This is

consistent with the finding of Navin S et al[107] where they have suspected the pro-oxidant role of uric acid in causation of oxidative stress leading to diabetic complication like diabetic retinopathy, though they could not clearly state that the hyperuricemia in diabetic retinopathy is either a protective response (due to its antioxidant role) or a primary cause of it (due to its pro-oxidant role).[103] In our study we found that out of the 50 patients with micro-vascular complications 19 (38%) had retinopathy and out of this 7 patients (36.84%) had increased uric acid levels. This was also corroborated with a study conducted by Ching-Chao Liang et al.,where he concluded that there was increased serum uric acid levels which correlated with the severity of diabetic Retinopathy.[104]

In another study by JavadKiani et al., he showedthat there was increased level of serum uric acid in diabetic patientswith diabetic neuropathy.[105]How ever in our study we found that there was no significant correlation between uric acid levels and diabetic neuropathy.

In a study conducted by YiliXu et al. he concluded that the patients with vascular complications had increased serum uric acid levels. He also said that this could be an independent predictor of vascular complications.[106]We found similar results in our study in which out of 50 patients with vascular complications there were 15 patients (30 %) with

increased levels of uric acid as opposed to only 8 patients (16%) in patients without microvascular complications.

Ito H. et al [97] demonstrated that HUA is associated with both microvascular and macrovascular complications of DM which was similar to the results of our study which showed that uric acid levels are raised in diabetic patients with microvascular complications. However, macrovascular complications were not assessed in our study.

Nazir Shah et al.[98] conducted a study in 2013 in 163 patients of diabetes mellitus (type 2) and proposed that elevation in the levels of uric acid was more in the diabetic patients with nephropathy (50%). In our study, it was found that 42% of patients with diabetic nephropathy had hyperuricemia which was similar to the study done by Nazir Shah et al.

In a study conducted in 60 diabetic patients by Nasri et al. [99], it was proved that there was a significant association between diabetic nephropathy and the levels of uric acid in the patient's serum which was in accordance with the results of our study.

PetterBjornstadet al[100] stated that there is a relation between the uric acid level elevation and development of diabetic nephropathy which was also noted in our study.

Su-Mi Kim et al.[101] demonstrated that HUA contributes to the development of nephropathy in diabetic patients. In our study, we found that 8 out of 19 patients with diabetic nephropathy had elevated uric acid levels.

In a study conducted by NS Nekiet al.[102] in 400 diabetic patients, it was shown that there is a linear correlation between serum uric acid and development of nephropathy in patients with diabetes, which was also proved in the study done by us.

Limitations of our study:

- Small sample size
- Macrovascular complications were not assessed
- Contribution of drugs to Hyperuricemia not assessed.

CONCLUSION

Hyperuricemia is one of the most sensitive indicators of microvascular complications caused due to Diabetes mellitus.[96]We conclude that there is a significant association of hyperuricemia and microvascular complications in patients with diabetes mellitus. Moreover, elevation in the uric acid levels was very strongly associated with nephropathy and retinopathy when compared to neuropathy. Therefore, early diagnosis and management of hyperuricemia is of utmost importance in the avoidance and management of diabetic complications.

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ABBREVIATIONS

DM	**Diabetes Mellitus**
UA	**Uric Acid**
SUA	**Serum Uric Acid**
HUA	**Hyperuricemia**
DR	**Diabetic Retinopathy**
DN	**Diabetic Nephropathy**
CKD	**Chronic kidney disease**
ADA	**American diabetes association**
WHO	**World health organization**
FBS	**Fasting blood sugar**
PPBS	**Post prandial blood sugar**
XDH	**Xanthine Dehydrogenase**
XO	**Xanthine Oxidase**
OAT	**Organic anion transporter**
NaDC3	**N-acetyleaspartate dicarboxylate co-transporter**
BMI	**Body mass index**
NPDR	**Non proliferative diabetic retinopathy**
SUA	**Serum uric acid**

PSG Institute of Medical Science and Research, Coimbatore

Institutional Human Ethics Committee

INFORMED CONSENT FORMAT FOR RESEARCH PROJECTS

(strike off items that are not applicable)

I DR Prashanth Arun, am carrying out a study on the topic:IsHyperuricemia a risk factor for vascular complications in patients with diabetes as part of our research project being carried out under the aegis of the Department of General Medicine.

My research guide is: Dr.Sujayamenon

The justification for this study is: To evaluate Hyperuricemia as an associated risk factor for vascular complications in patients with diabetes.

The objectives of this study are:

Primary Objective:To evaluate hyperuricemia as an associated risk factor for vascular complications in patients with diabetes.

Sample size: 100

Study volunteers / participants :

1). Patients with diabetes

2).Age >20<80years

Location: PSG Hospitals

We request you to kindly cooperate with us in this study. We propose collect background information and other relevant details related to this study. We will be carrying out:

Data collected will be stored for a period of 10 years. We will / will not use the data as part of another study.

INITIAL INTERVIEW: Approximately 15 minutes

Clinical examination will be done to asses other clinical findings…for example CNS examination to rule out Diabetic neuropathy.

Methodology: . The study will be conducted in PSG Hospital

Observational Study

- Diagnosis of Diabetes by ADA criteria's
- Patients examined for vascular complications
- Dividing them into 2 groups
- .Patients with diabetes and patients with diabetes and vascular complications
- Uric acid levels will be observed for both the groups.
- .Age, sex, duration of the disease will be all most equal in both the groups.
- .Result will be if Hyperuricemia is an added risk factor for vascular complications in a diabetic patient.

Benefits from this study: To early diagnose risk factor for vascular complication in a diabetic patient.

Risks involved by participating in this study:NIL

How the **results** will be used:

If you are uncomfortable in answering any of our questions during the course of the interview / biological sample collection, **you have the right to withdraw from the interview / study at anytime.** You have the freedom to withdraw from the study at any point of time. Kindly be assured that your refusal to participate or withdrawal at any stage, if you so decide, will not result in any form of

compromise or discrimination in the services offered nor would it attract any penalty. You will continue to have access to the regular services offered to a patient. You will **NOT** be paid any remuneration for the time you spend with us for this interview / study. The information provided by you will be kept in strict confidence. Under no circumstances shall we reveal the identity of the respondent or their families to anyone. The information that we collect shall be used for approved research purposes only. You will be informed about any significant new findings - including adverse events, if any, – whether directly related to you or to other participants of this study, developed during the course of this research which may relate to your willingness to continue participation.

Consent: The above information regarding the study, has been read by me/ read to me, and has been explained to me by the investigator/s. Having understood the same, I hereby give my consent to them to interview me. I am affixing my signature / left thumb impression to indicate my consent and willingness to participate in this study (i.e., willingly abide by the project requirements).

Signature / Left thumb impression of the Study Volunteer / Legal Representative:

Signature of the Interviewer with date: Witness:

Contact number of PI: 9940530630

Contact number of Ethics Committee Office: 0422 2570170 Extn.: 5818

ஒப்புதல் படிவம்

தேதி :

பிரசாந்த் அருண் ஆகிய நான் PSG மருத்துவக் கல்லூரியின் பொது மருத்துவ துறையின் கீழ் இரத்தத்தில் யூரிக் அமிலமின் அளவு அதிகமாவதால் நீரிழிவு நோயாளிகளுக்கு இரத்தகுழாயில் ஏற்படும் பின்விளைவுகளுக்கு தொடர்பு உள்ளதா என்ற தலைப்பில் ஆய்வு மேற்கொள்ள உள்ளேன்.

என் ஆய்வு வழிகாட்டி: மரு.சஜயா மேனன் MD

ஆய்வு மேற்கொள்வதற்கான அடிப்படை: இரத்தத்தில் யூரிக் அமிலமின் அளவு அதிகமாவதால் நீரிழிவு நோயாளிகளுக்கு இரத்தகுழாயில் ஏற்படும் பின்விளைவுகளுக்கு தொடர்பை அறிவதன் மூலம் நீரிழிவு நோயாளிகளுக்கு இரத்தகுழாயில் ஏற்படும் பின்விளைவுகளை அறிந்து சிகிச்சை அளிக்க முடியும். அதன் மூலம் நோய் வாய்ப்படுபவர்களின் எண்ணிக்கையையும், இறப்பும் குறைக்க முடியும்.

ஆய்வின் நோக்கம்: நீரிழிவு நோயாளிகளுக்கு இரத்தகுழாயில் ஏற்படும் பின்விளைவுகளை முன்கூட்டியே அறிந்து பின்விளைவுகளை தடுக்கலாம் .

ஆய்வில் பங்கு பெறும் நபர்களின் எண்ணிக்கை: 120

ஆய்வு மேற்கொள்ளும் இடம் : PSG மருத்துவமனை, பீளமேடு, கோவை

ஆய்வின் பலன்கள் :
நீரிழிவு நோயாளிகளுக்கு ஏற்படும் பின்விளைவுகளுக்கான் காரணம் அறிந்து சிகிச்சை அளிக்க முடியும்.

ஆய்வினால் ஏற்படும் அசௌகரியங்கள்/ பக்க விளைவுகள்: எதுவும் இல்லை

இந்த ஆய்வில் கிடைக்கும் தகவல்கள் இரண்டு வருடங்கள் பாதுகாக்கப்படும். இவை வேறு எந்த ஆய்விற்கும் பயன்படுத்தப் பட மாட்டாது. எந்த நிலையிலும் உங்களைப் பற்றிய தகவல்கள் யாருக்கும் தெரிவிக்கப்பட மாட்டாது. அவை இரகசியமாக வைக்கப்படும்.

இந்த ஆய்வில் பங்கேற்க ஒப்புக்கொள்ளுவதால் எந்த விதமான் பலனும் உங்களுக்கு கிடைக்காது. எந்த நேரத்தில் வேண்டுமானாலும் ஆய்விலிருந்து விலகிக்கொள்ளும் உரிமை உங்களுக்கு உண்டு. ஆய்விலிருந்து விலகிக்கொள்வதால் உங்களுக்கு அளிக்கப்படும் சிகிச்சையில் எந்த வித மாற்றமும் இருக்காது.

இந்த ஆராய்ச்சிக்காக உங்களிடம் சில கேள்விகள் கேட்கப்படும் / சில இரத்த மாதிரிகள் எடுக்கப்படும்.

மேலும், இந்த ஆய்வில் பங்கு கொள்வது உங்கள் சொந்த விருப்பம். இதில் எந்த விதக் கட்டாயமும் இல்லை. நீங்கள் விருப்பப் பட்டால், இந்த ஆய்வின் முடிவுகள் உங்களுக்குத் தெரியப் படுத்தப்படும்.

ஆய்வாளரின் கையொப்பம் :

தேதி :

ஆய்வுக்குட்படுபவரின் ஒப்புதல்:
நான் இந்த ஆராய்ச்சியின் நோக்கம் மற்றும் அதன் பயன்பாட்டினைப் பற்றி தெளிவாகவும், விளக்கமாகவும் தெரியப்படுத்தப் பட்டுள்ளேன். இந்த ஆராய்ச்சியில் பங்கு கொள்ளவும். இந்த ஆராய்ச்சியின் மருத்துவ ரீதியான குறிப்புகளை வரும் காலத்தில் உபயோகப்படுத்திக் கொள்ளவும் முழு மனதுடன் சம்மதிக்கிறேன்.

ஆய்வுக்குட்படுபவரின் பெயர், முகவரி :

கையொப்பம் :

தேதி :

ஆய்வாளரின் தொலைபேசி எண் :
மனித நெறிமுறைக் குழு அலுவலகத்தின் தொலைபேசி : 0422 2570170 Extn:5818

VARIABLES RECORDED

Name: Age: OP No.

Gender: Occupation:

Duration of Diabetes:

FBS:

PPBS:

SERUM URIC ACID:

MICRO VASCULAR COMPLICATIONS: YES/NO

IF yes

WHAT COMPLICATION:

MASTER CHART (PATIENTS WITH COMPLICATIONS)

S. NO	AGE/SEX	D.RETINOPATHY	D.NEPHROPATHY	D.NEUROPATHY	HBAIC	FBS	PPBS	URIC ACID
	55/M	**NO**	**YES**	**NO**	**8.7**	**105**	**152**	**10.2**
2	**64/M**	**NO**	**YES**	**NO**	**6.4**	**97**	**175**	**6.9**
3	**38/F**	**YES**	**NO**	**NO**	**6.3**	**148**	**158**	**8.4**
4	**55/M**	**YES**	**NO**	**NO**	**8.7**	**105**	**152**	**8.7**
5	**53/F**	**NO**	**YES**	**NO**	**6.2**	**98**	**189**	**6.9**
6	**49/M**	**YES**	**NO**	**NO**	**5.9**	**97**	**136**	**7.8**
7	**49/M**	**NO**	**YES**	**NO**	**5.9**	**97**	**136**	**7.8**
8	**M/62**	**NO**	**YES**	**NO**	**10.2**	**100**	**193**	**8**
9	**M/43**	**YES**	**NO**	**NO**	**6.5**	**133**	**186**	**7**
10	**M/55**	**YES**	**NO**	**NO**	**14**	**95**	**162**	**2.5**
11	**F/48**	**NO**	**NO**	**YES**	**7.6**	**125**	**194**	**5.3**
12	**F/42**	**YES**	**NO**	**NO**	**10.2**	**125**	**200**	**4.2**
13	**F/42**	**NO**	**YES**	**NO**	**10.2**	**125**	**200**	**4.2**
14	**M/54**	**YES**	**NO**	**NO**	**9**	**127**	**135**	**3.8**
15	**M/55**	**NO**	**YES**	**NO**	**7.2**	**100**	**183**	**5.3**
16	**M/64**	**NO**	**NO**	**YES**	**10.1**	**130**	**147**	**5.3**
17	**F/49**	**YES**	**NO**	**NO**	**6.6**	**102**	**131**	**9.2**
18	**F/65**	**NO**	**NO**	**YES**	**5.8**	**100**	**158**	**4**
19	**M/50**	**YES**	**NO**	**NO**	**7.2**	**74**	**130**	**5.4**
20	**M/69**	**NO**	**YES**	**NO**	**6.9**	**300**	**387**	**9.2**
21	**M/60**	**NO**	**YES**	**NO**	**9.6**	**107**	**200**	**4.2**
22	**M/53**	**NO**	**NO**	**YES**	**8**	**189**	**208**	**6.4**
23	**F/57**	**NO**	**NO**	**YES**	**11.1**	**95**	**194**	**2.5**

24	**55/F**	**YES**	**NO**	**NO**	**9.8**	**179**	**200**	**3.9**
25	**55/F**	**NO**	**NO**	**YES**	**14**	**209**	**326**	**3.9**
26	**60/F**	**YES**	**NO**	**NO**	**8.7**	**216**	**343**	**5.2**
27	**50/F**	**NO**	**NO**	**YES**	**7.1**	**126**	**259**	**3.9**
28	**71/F**	**YES**	**YES**	**YES**	**7.7**	**106**	**300**	**6**
29	**71/F**	**YES**	**YES**	**YES**	**7.7**	**106**	**300**	**6**
30	**64/F**	**YES**	**NO**	**NO**	**11.7**	**212**	**224**	**2.9**
31	**66/F**	**NO**	**YES**	**NO**	**6.46**	**126**	**201**	**9.2**
32	**52/M**	**NO**	**YES**	**NO**	**8.9**	**89**	**197**	**5.2**
33	**50/F**	**NO**	**YES**	**NO**	**8.2**	**143**	**179**	**3.7**
34	**45/M**	**NO**	**YES**	**NO**	**8.5**	**150**	**205**	**4.5**
35	**60/M**	**NO**	**YES**	**NO**	**8.9**	**110**	**197**	**5.2**
36	**70/M**	**NO**	**NO**	**YES**	**6.7**	**130**	**220**	**5.9**
37	**60/F**	**NO**	**NO**	**YES**	**8.23**	**120**	**179**	**3.7**
38	**71/F**	**NO**	**NO**	**YES**	**7.7**	**176**	**300**	**5.9**
39	**61/M**	**NO**	**NO**	**YES**	**6.4**	**178**	**224**	**4.4**
40	**60/M**	**NO**	**NO**	**YES**	**7.4**	**240**	**329**	**4.4**
41	**70/F**	**YES**	**NO**	**NO**	**7.7**	**176**	**300**	**5.9**
42	**70/M**	**YES**	**NO**	**NO**	**7.15**	**163**	**234**	**4.6**
43	**70/F**	**NO**	**NO**	**YES**	**13.2**	**152**	**201**	**4**
44	**60/F**	**YES**	**NO**	**NO**	**7.19**	**164**	**204**	**4.5**
45	**F/49**	**YES**	**NO**	**NO**	**6.6**	**102**	**131**	**9.2**
46	**50/M**	**NO**	**YES**	**NO**	**8.7**	**158**	**254**	**10.2**
47	**M/48**	**NO**	**YES**	**NO**	**8**	**180**	**250**	**9.2**
48	**F/54**	**NO**	**YES**	**NO**	**6.46**	**125**	**200**	**9.2**
49	**40/F**	**YES**	**NO**	**NO**	**6.7**	**145**	**248**	**8.4**
50	**F/42**	**NO**	**NO**	**YES**	**10.2**	**134**	**195**	**4.2**

MASTER CHART (PATIENTS WITHOUT COMPLICATIONS)

S No.	AGE	COMPLICATION	HBAIC	FBS	PPBS	URIC ACID
1	M/58	NO	10.2	207	227	4.2
2	M/68	NO	7.7	123	252	4.9
3	M/70	NO	9.17	101	230	1.7
4	m/65	NO	8.9	126	157	5.1
5	m/60	NO	7	110	183	5.4
6	M/60	NO	6.3	97	162	5.8
7	M/52	NO	7	127	142	8.1
8	M/50	NO	5.4	96	120	2.9
9	F/65	NO	6.4	127	154	1.4
10	m/70	NO	7	90	131	2.8
11	F/70	NO	6.6	80	200	5.4
12	F/65	NO	5.7	87	112	5.5
13	m/55	NO	6.3	132	150	5.5
14	M/60	NO	6.1	85	153	6.8
15	M/50	NO	8.9	190	220	2.1
16	M/62	NO	8.9	72	120	3.3
17	F/70	NO	6.1	82	172	4.1
18	M/60	NO	6	115	132	2
19	m/62	no	10.2	108	193	8
20	m/69	no	6.8	76	152	1.8
21	m/70	no	10.7	108	266	4.3
22	m/45	no	6.5	119	155	6.6
23	m/64	no	10.7	138	164	2.4
24	m67	no	6.5	100	174	4.4
25	m/42	no	5.1	114	136	7.8

26	m/56	no	6.8	114	136	5
27	m/64	no	7.5	96	200	9.4
28	m/71	no	6.3	109	123	10.7
29	m/52	no	7.2	159	234	6.3
30	M/40	NO	8.8	190	250	5.3
31	M/38	no	6.9	196	287	5.3
32	60/m	no	10.2	200	276	4.3
33	68/m	no	7.1	121	250	3.6
34	50/m	no	7.7	150	210	5
35	75/m	no	10.1	188	190	2.8
36	77/m	no	7.2	255	171	5.3
37	68/m	no	7	143	144	5.7
38	46/m	no	7.3	112	144	6.2
39	80/m	no	6.5	153	282	6.1
40	57/m	no	8.6	121	158	7
41	55/f	no	7.9	193	156	7.7
42	54/f	no	6.3	124	130	2.8
43	60/f	no	6.4	185	159	2.8
44	73/f	no	6.1	102	180	9.2
45	38/f	no	6.1	102	180	9.2
46	m/70	no	8.6	119	138	5.1
47	53/f	no	7.5	146	196	4.2
48	52/f	no	8.12	293	345	3.8
49	66/f	no	10.2	161	237	4.2
50	60/m	no	10.2	103	198	4.2